**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | | |
|---|---|---|
| TRISTRATA TECHNOLOGY, INC., | ) | |
| | ) | |
| Plaintiff, | ) | |
| | ) | |
| v. | ) | Civil Action No. |
| | ) | |
| JEUNIQUE INTERNATIONAL, INC., DERMALOGICA, INC., GLYCOFORM-D CORP., AND JUVENSES BY ELAINE GAYLE, INC., | ) | |
| | ) | |
| Defendants. | ) | **JURY DEMAND** |

**COMPLAINT**

Plaintiff, TriStrata Technology, Inc. ("TTI"), by its attorneys, Mayer, Brown, Rowe & Maw, alleges for its Complaint against Defendants on knowledge as to itself and its own acts and upon information and belief as to all other matters, as follows:

**SUMMARY OF COMPLAINT**

1. This is an action for patent infringement pursuant to the patent laws of the United States, 35 U.S.C. §100, *et seq.* arising out of Defendant's willful and deliberate infringement of the patents described below.

2. The patents were issued to Drs. Eugene J. Van Scott and Ruey J. Yu, who are pioneers in the field of the use of alpha hydroxyacids for the treatment of conditions associated with the skin. Each of the patents describes and claims a method of using a composition containing an alpha hydroxyacid to treat and/or reduce skin conditions including but not limited to wrinkles, fine lines and other conditions affecting human skin. (The four patents at issue in this suit are collectively referred to as the "TTI Patents.")

3. TTI provided notice of the TTI Patents to manufacturers, sellers and/or distributors of cosmetic products both in the United States and abroad. The notice explicitly informed the recipients, among other things, that: (i) the TTI Patents had been issued and assigned to TTI; and (ii) TTI was willing to enter into a licensing agreement. To date, several of the largest manufacturers and/or marketers in the cosmetics industry have entered into such license agreements with TTI, including, without limitation, Avon, Johnson and Johnson, Chesebrough Pond's, Elizabeth Arden, Allergan, Beiersdorf, Inc., L'Oreal, Chanel, Neoteric Cosmetics, Inc., and Erno Laszlo, and TTI has received substantial royalty payments in return for granting such licenses.

4. However, Defendants have continued to refuse to recognize the TTI Patents and have willfully and deliberately infringed the TTI Patents by, among other things, promoting the use of their products through national advertisements and websites and otherwise in a manner designed to induce infringement of the TTI Patents.

## JURISDICTION AND VENUE

5. This Court has jurisdiction over this action pursuant to 28 U.S.C. §§1331 and 1338(a).

6. Venue is proper in this District pursuant to 28 U.S.C. §1391(b) and (c) and 28 U.S.C. §1400(b).

## THE PARTIES

### The Plaintiff

7. Plaintiff TTI is a Delaware corporation with its principal place of business at 1105 North Market Street, Suite 1300, P.O. Box 8985, Wilmington, Delaware 19899. TTI is in the business of developing and licensing novel dermatological, pharmaceutical and skin care product

technology. TTI is the assignee of certain patents issued to Drs. Van Scott and Yu ("the Inventors").

**The Defendants**

8. Defendant Jeunique International, Inc. (hereinafter "Jeunique") is a California corporation with its principal place of business in California. Jeunique is in the business of manufacturing, distributing, and/or selling cosmetic products in this District and elsewhere in the United States.

9. Defendant Dermalogica, Inc. (hereinafter "Dermalogica") is a California corporation with its principal place of business in California. Dermalogica is in the business of manufacturing, distributing, and/or selling cosmetic products in this District and elsewhere in the United States.

10. Defendant Glycoform-D Corp. (hereinafter "Glycoform-D") is a Florida corporation with its principal place of business in Florida. Glycoform-D is in the business of manufacturing, distributing, and/or selling cosmetic products in this District and elsewhere in the United States.

11. Defendant Juvenesse By Elaine Gayle, Inc. (hereinafter "Juvenesse") is an Illinois corporation with its principal place of business in Illinois. Juvenesse is in the business of manufacturing, distributing, and/or selling cosmetic products in this District and elsewhere in the United States.

**THE PATENTS**

12. On February 25, 1992, United States Letters Patent No. 5,091,171 entitled "Amphoteric Composition and Polymeric Forms of Alpha Hydroxyacids and Their Therapeutic Use" was duly and legally issued to the Inventors and assigned to TTI. On September 26, 1995, the PTO completed a re-examination of U.S. Patent No. 5,091,171. Thereafter, on July 15,

1997, the PTO completed a second re-examination of U.S. Patent No. 5,091,171 and issued Re-examination Certificate B2 5,091,171. A copy of this patent and its two Re-examination Certificates (collectively "the '171 Patent") are annexed hereto as Exhibit A. The '171 Patent describes and claims a method for treating wrinkles by topically applying a composition comprising an alpha hydroxyacid.

13. On August 20, 1996, United States Letters Patent No. 5,547,988, entitled "Alleviating Signs of Dermatological Aging with Glycolic Acid, Lactic Acid or Citric Acid" was duly and legally issued to the Inventors and assigned to TTI. On July 15, 1997, the PTO completed a re-examination of U.S. Patent No. 5,547,988 and issued Re-examination Certificate B1 5,547,988, in which all of the original claims were confirmed without change. A copy of this patent and its Re-examination Certificate (collectively "the '988 Patent") are annexed hereto as Exhibit B. The '988 Patent describes and claims a method for reducing the appearance of skin changes associated with aging by topically applying a composition comprising a glycolic acid, lactic acid or citric acid or a topically effective salt thereof, to the area of skin exhibiting the sign of aging.

14. On January 31, 1995, United States Letters Patent No. 5,385,938, entitled "Method of Using Glycolic Acid for Treating Wrinkles" was duly and legally issued to the Inventors and assigned to TTI. On July 15, 1997, the U.S. Patent and Trademark Office ("PTO") completed a re-examination of U.S. Patent No. 5,385,938 and issued Re-examination Certificate B1 5,385,938, in which all of the original claims were confirmed without change. A copy of this patent and its re-examination certificate (collectively "the '938 Patent") are annexed hereto as Exhibit C. The '938 Patent describes and claims a method for visibly reducing a human facial

wrinkle by topically applying a composition comprising glycolic acid and/or a topically effective salt thereof, to the wrinkle.

15. On February 14, 1995, United States Letters Patent No. 5,389,677, entitled "Method of Treating Wrinkles Using Glycolic Acid" was duly and legally issued to the Inventors and assigned to TTI. On July 15, 1997, the PTO completed a re-examination of U.S. Patent No. 5,389,677 and issued Re-examination Certificate B1 5,389,677, in which all of the original claims were confirmed without change. A copy of this patent and its re-examination certificate (collectively "the '677 Patent") are annexed hereto as Exhibit D. The '677 Patent describes and claims a method for visibly reducing any type of human skin wrinkle by topically applying a composition comprising glycolic acid and/or a topically effective salt thereof, to the wrinkle.

16. TTI is the assignee of the '171, '988, '938 and '677 Patents.

17. TTI's methods for reducing wrinkles and other skin conditions associated with aging, as described and claimed in the annexed patents, have enjoyed excellent commercial success since their introduction. Indeed, TTI's methods have become the methods of choice for the consuming public for reducing wrinkles, fine lines and other visible effects of aging on the human skin.

**FIRST CLAIM FOR RELIEF**
**(Infringement of the '171 Patent)**

18. TTI repeats and realleges the allegations of paragraphs 1 through 17 as if fully set forth herein.

19. Defendants are engaged in the manufacture, distribution and/or sale of cosmetic products comprising alpha hydroxyacids, and/or a topically effective salt thereof. These products are sold and promoted over the Internet, through national advertisements, websites and/or through other marketing materials that encourage prospective customers to apply such

products to their skin for the purpose of visibly reducing a human skin wrinkle and/or fine lines on the human skin.

20. By virtue of these promotional activities, Defendants have been contributing, and continue to contribute, to and/or to induce the infringement of the '171 Patent in violation of 35 U.S.C. §271.

21. TTI is informed and believes that Defendants have received express notice of the '171 Patent in a letter and/or had prior knowledge of that patent prior to the filing of this complaint. Despite notice, Defendants have failed to enter into a license agreement, and continue to contribute and/or induce infringement of the '171 Patent in violation of 35 U.S.C. §271.

22. TTI is informed and believes that Defendants' actions have been willful and deliberate, entitling TTI to increased damages under 35 U.S.C. §284 and making this an exceptional case within the meaning of 35 U.S.C. §285.

**SECOND CLAIM FOR RELIEF**
**(Infringement of the '988 Patent)**

23. TTI repeats and realleges the allegations of paragraphs 1 through 22 as if fully set forth herein.

24. Defendants are engaged in the manufacture, distribution and/or sale of cosmetic products comprising alpha hydroxyacids, including but not limited to, glycolic acid and/or a topically effective salt thereof. These products are sold and promoted over the Internet through national advertisements, websites and/or through other marketing materials that encourage prospective customers to apply such products to their skin for the purpose of visibly reducing a human skin wrinkle and/or fine lines on the human skin.

25. By virtue of these promotional activities, Defendants have been contributing, and continue to contribute, to and/or to induce the infringement of the '988 Patent in violation of 35 U.S.C. §271.

26. TTI is informed and believes that Defendants have received express notice of the '988 Patent and/or had prior knowledge of that patent prior to the filing of this complaint. Despite notice, Defendants have failed to enter into a license agreement, and continue to contribute and/or induce infringement of the '988 Patent in violation of 35 U.S.C. §271.

27. TTI is informed and believes that Defendants' actions have been willful and deliberate, entitling TTI to increased damages under 35 U.S.C. §284 and making this an exceptional case within the meaning of 35 U.S.C. §285.

**THIRD CLAIM FOR RELIEF**
**(Infringement of the '938 Patent)**

28. TTI repeats and realleges the allegation of paragraphs 1 through 27 as if fully set forth herein.

29. Defendants are engaged in the manufacture, distribution and/or sale of cosmetic products comprising alpha hydroxyacids, including but not limited to, glycolic acid and/or a topically effective salt thereof. These products are sold and promoted over the Internet, through national advertisements, websites and/or through other marketing materials that encourage prospective customers to apply such products to their skin for the purpose of visibly reducing a human skin wrinkle and/or fine lines on the human skin.

30. By virtue of these promotional activities, Defendants have been contributing, and continue to contribute, to and/or to induce the infringement of the '938 Patent in violation of 35 U.S.C. §271.

31. TTI is informed and believes that Defendants have received express notice of the '938 Patent and/or had prior knowledge of that patent prior to the filing of this complaint. Despite notice, Defendants have failed to enter into a license agreement, and continue to contribute and/or induce infringement of the '938 Patent in violation of 35 U.S.C. §271.

32. TTI is informed and believes that ICN's actions have been willful and deliberate, entitling TTI to increased damages under 35 U.S.C. §284 and making this an exceptional case within the meaning of 35 U.S.C. §285.

**FOURTH CLAIM FOR RELIEF**
**(Infringement of the '677 Patent)**

33. TTI repeats and realleges the allegations of paragraphs 1 through 32 as if fully set forth herein.

34. Defendants are engaged in the manufacture, distribution and/or sale of cosmetic products comprising alpha hydroxyacids, including but not limited to, glycolic acid and/or a topically effective salt thereof. These products are sold and promoted over the Internet, through national advertisements, websites and/or through other marketing materials that encourage prospective customers to apply such products to their skin for the purpose of visibly reducing a human skin wrinkle and/or fine lines on the human skin.

35. By virtue of these promotional activities, Defendants have been contributing, and continue to contribute, to and/or to induce the infringement of the '677 Patent in violation of 35 U.S.C. §271.

36. TTI is informed and believes that ICN has received express notice of the '677 Patent and/or had prior knowledge of that patent prior to the filing of this complaint. Despite notice, Defendants have failed to enter into a license agreement, and continue to contribute and/or induce infringement of the '677 Patent in violation of 35 U.S.C. §271.

37. TTI is informed and believes that Defendants' actions have been willful and deliberate, entitling TTI to increased damages under 35 U.S.C. §284 and making this an exceptional case within the meaning of 35 U.S.C. §285.

WHEREFORE, TTI prays that this Court:

A. Find that the '171, '988, '938 and '677 Patents have been infringed by the Defendants, as alleged herein;

B. Award damages adequate to compensate TTI for Defendants' infringements, but not less than a reasonable royalty for the use made of the claimed inventions by Defendants, together with interest, including pre-judgment interest, and costs as fixed by the Court;

C. Find that Defendants' infringements have been willful and deliberate;

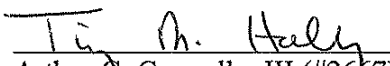
D. Award TTI increased damages and attorneys' fees pursuant to 35 U.S.C. §284 and §285 because of the willful and deliberate nature of Defendants' infringements;

E. Permanently enjoin Defendants and their officers, agents, servants, employees and affiliates, as well as all others in active concert or participation with it as any of the foregoing, from inducing or contributing to the infringement of the '171, '988, '938 and '677 Patents; and

F. Award TTI such other and further relief as this Court may deem just and proper.

Dated: October 17, 2006

Respectfully submitted,



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**JURY DEMAND**

Plaintiff hereby demands a TRIAL BY JURY as to all issues so triable.

Respectfully submitted,

October 17, 2006

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# EXHIBIT A
# (Part 1)

US005091171A

# United States Patent [19]

Yu et al.

[11] Patent Number: 5,091,171

[45] Date of Patent: Feb. 25, 1992

[54] **AMPHOTERIC COMPOSITIONS AND POLYMERIC FORMS OF ALPHA HYDROXYACIDS, AND THEIR THERAPEUTIC USE**

[76] Inventors: **Ruey J. Yu**, 4 Lindenwold Ave., Ambler, Pa. 19002; **Eugene J. Van Scott**, 3 Hidden La., Abington, Pa. 19001

[21] Appl. No.: **393,749**

[22] Filed: **Aug. 15, 1989**

[63] **Related U.S. Application Data**

This application is a continuation-in-part application of U.S. Application Serial No. 06/945,680, filed December 23, 1986, which was abandoned in favor of continuing application Serial No. 07/469,738, filed January 19, 1990, now pending.

[51] **Int. Cl.**[5] ..... **A61K 23/30**; A61K 31/70; A61K 31/66

[52] **U.S. Cl.** ..... **424/642**; 424/691; 514/2; 514/12; 514/19; 514/23; 514/114; 514/349; 514/399; 514/419; 514/518; 514/561; 514/562; 514/567; 514/532; 514/547; 514/558; 514/941

[58] **Field of Search** ..... 514/2, 12, 23, 114, 514/349, 399, 419, 518, 561, 562, 567, 947, 532, 547, 558, 19; 424/642, 691

[56] **References Cited**

U.S. PATENT DOCUMENTS

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|---|---|---|---|
| 3,920,835 | 11/1975 | Van Scott et al. | 514/557 |
| 4,105,782 | 8/1978 | Yu et al. | 514/557 |
| 4,363,815 | 12/1982 | Yu et al. | 514/557 |
| 4,929,722 | 5/1990 | Partain et al. | 514/947 |

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| | | |
|---|---|---|
| 80178 | 4/1975 | South Africa . |

OTHER PUBLICATIONS

Juhlin, et al. Ger. Offenlegungshift 2,517,413, Chemical Abstracts vol. 84, 1976 Abs. 79710x.

*Primary Examiner*—Mukund J. Shah
*Assistant Examiner*—E. C. Ward
*Attorney, Agent, or Firm*—Foley & Lardner

[57] **ABSTRACT**

Preventive as well as therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxyacids, alpha ketoacids, related compounds or polymeric forms of hydroxyacids is disclosed. The cosmetic conditions and the dermatologic disorders in which the amphoteric compositions and the polymeric compounds may be useful include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, kyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging, and skin requiring cleansers.

**20 Claims, No Drawings**

# AMPHOTERIC COMPOSITIONS AND POLYMERIC FORMS OF ALPHA HYDROXYACIDS, AND THEIR THERAPEUTIC USE

This application is a continuation-in-part application of U.S. Application Serial No. 06/945,680, filed December 23, 1986, which was abandoned in favor of continuing application Serial No. 07/469,738, filed January 19, 1990, now pending.

## FIELD OF THE INVENTION

This invention relates generally to therapeutic treatment as well as preventive measures for cosmetic conditions and dermatologic disorders by topical administration of amphoteric compositions or polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds. We initially discovered that alpha hydroxy or keto acids and their derivatives were effective in the topical treatment of disease conditions such as dry skin, ichthyosis, eczema, palmar and plantar hyperkeratoses, dandruff, acne and warts.

We have now discovered that amphoteric compositions and polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds on topical administration are therapeutically effective for various cosmetic conditions and dermatologic disorders.

## BRIEF DESCRIPTION OF THE PRIOR ART

In our prior U.S. Pat. No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoses" we described and claimed the use of certain alpha hydroxyacids, alpha ketoacids and related compounds for topical treatment of fish-scale like ichthyotic conditions in humans. In our U.S. Pat. No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of these alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis.

In our prior U.S. Pat. No. 4,105,783 entitled "Treatment of Dry Skin" we described and claimed the use of alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dry skin. In our recent U.S. Pat. No. 4,246,261 entitled "Additives Enhancing Topical Corticosteroid Action" we described and claimed that alpha hydroxyacids, alpha ketoacids and their derivatives, could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis and other inflammatory skin conditions.

In our more recent U.S. Pat. No. 4,363,815 entitled "Alpha Hydroxyacids, Alpha Ketoacids and Their Use in Treating Skin Conditions" we described and claimed that alpha hydroxyacids and alpha ketoacids related to or originating from amino acids, whether or not found in proteins, were effective in topical treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier's disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema, pruritus, warts and herpes.

In our most recent patent application Ser. No. 945,680 filed Dec. 23, 1986 and entitled "Additives Enhancing Topical Actions of Therapeutic Agents" we described and claimed that incorporation of an alpha hydroxyacid or related compound can substantially enhance therapeutic actions of cosmetic and pharmaceutical agents.

## SUMMARY OF THE INVENTION

There is no doubt that alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatment of various cosmetic conditions and dermatologic disorders including dry skin, acne, dandruff, keratoses, age spots, wrinkles and disturbed keratinization. However, the compositions containing these acids may irritate human skin on repeated topical applications due to lower pH of the formulations. The irritation may range from a sensation of tingling, itching and burning to clinical signs of redness and peeling. Causes for such irritation may arise from the following:

Upper layers of normal skin have a pH of 4.2 to 5.6, but the compositions containing most alpha hydroxyacids or alpha ketoacids have pH values of less than 3.0. For example, a topical formulation containing 7.6% (1 M) glycolic acid has a pH of 1.9, and a composition containing 9% (1 M) lactic acid has the same pH of 1.9. These compositions of lower pH on repeated topical applications can cause a drastic pH decrease in the stratum corneum of human skin, and provoke disturbances in intercorneocyte bondings resulting in adverse skin reactions, especially to some individuals with sensitive skin.

Moreover, with today's state of the art it is still very difficult to formulate a lotion, cream or ointment emulsion which contains a free acid form of the alpha hydroxyacid, and which is physically stable as a commercial product for cosmetic or pharmaceutical use.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with a metallic alkali such as sodium hydroxide or potassium hydroxide the composition becomes therapeutically ineffective. The reasons for such loss of therapeutic effects are believed to be as follows:

The intact skin of humans is a very effective barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by oral or other systematic administration, but many of them are much less or totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors; (a) bioavailability of the active ingredient in the topical preparation and (b) percutaneous absorption, penetration and distribution of the active ingredient to the target site in the skin. For example, a topical preparation containing 5% salicylic acid is therapeutically effective as a keratolytic, but that containing 5% sodium salicylate is not an effective product. The reason for such difference is that salicylic acid is in bioavailable form and can penetrate the stratum corneum, but sodium salicylate is not in bioavailable form and cannot penetrate the stratum corneum of the skin.

In the case of alpha hydroxyacids, a topical preparation containing 5% glycolic acid is therapeutically effective for dry skin, but that containing 5% sodium glycollate is not effective. The same is true in case of 5% lactic acid versus 5% sodium lactate. The reason for such difference is that both glycolic acid and lactic acid are in bioavailable forms and can readily penetrate the stratum corneum, but sodium glycollate and sodium lactate are not in bioavailable forms and cannot penetrate the stratum corneum of the skin.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with ammonium hydroxide or an organic base of smaller molecule the composition still shows some therapeutic effects for certain cosmetic conditions such as dry skin, but the composition has lost most of its potency for other dermatologic disorders such as wrin-

kles, keratoses, age spots and skin changes associated with aging.

It has now been discovered that amphoteric compositions containing alpha hydroxyacids, alpha ketoacids or related compounds, and also the compositions containing dimeric or polymeric forms of hydroxyacids overcome the aforementioned shortcomings and retain the therapeutic efficacies for cosmetic conditions and dermatologic disorders. The amphoteric composition contains in combination an amphoteric or pseudoamphoteric compound and at least one of the alpha hydroxyacids, alpha ketoacids or related compounds. Such amphoteric system has a suitable pH, and can release the active form of an alpha hydroxyacid or alpha ketoacid into the skin. The dimeric and polymeric forms of alpha, beta or other hydroxyacids in non-aqueous compositions have a more desired pH than that of the monomeric form of the hydroxyacids. The non-aqueous compositions can be formulated and induced to release the active form of hydroxyacids after the compositions have been topically applied to the skin. The cosmetic conditions and dermatologic disorders in humans and animals, in which the amphoteric compositions containing the dimeric or polymeric forms of hydroxyacids may be useful, include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, hyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging and as skin cleansers.

## DETAILED DESCRIPTION OF THE INVENTION

### I. Amphoteric and Pseudoamphoteric Compositions

Amphoteric substances by definition should behave either as an acid or a base, and can be an organic or an inorganic compound. The molecule of an organic amphoteric compound should consist of at least one basic and one acidic group. The basic groups include, for example, amino, imino and guanido groups. The acidic groups include, for example, carboxylic, phosphoric and sulfonic groups. Some examples of organic amphoteric compounds are axino acids, peptides, polypeptides, proteins, creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine and deacetylated chondroitin.

Inorganic amphoteric compounds are certain metallic oxides such as aluminum oxide and zinc oxide.

Pseudoamphoteric compounds are either structurally related to true amphoteric compounds or capable of inducing the same function when they are incorporated into the compositions containing alpha hydroxyacids or ketoacids. Some examples of pseudoamphoteric compounds are creatinine, stearamidoethyl diethylamine, stearamidoethyl diethanolamine, stearamidopropyl dimethylamine, quaternary ammonium hydroxide and quaternium hydroxide.

The amphoteric composition of the instant invention contains in combination an alpha hydroxyacid or alpha ketoacid and an amphoteric or pseudoamphoteric compound. There are two advantages of utilizing an amphoteric or the like compound in the therapeutic composition containing an alpha hydroxy or ketoacid. These are (a) the overall pH of the composition is raised, so that the composition becomes less or non-irritating to the skin and (b) some alpha hydroxy or ketoacid molecules react with the amphoteric compound to form a quadruple ionic complex which acts as buffering system to control the release of alpha hydroxy or ketoacid into the skin, therefore, eliminating the skin irritation and still retaining the therapeutic efficacies.

The following are some examples. 2-Hydroxyethanoic acid (glycolic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.0 and 3.2 when arginine 0.5 M and creatinine 0.5 M respectively are incorporated into the formulations. 2-Hydroxypropanoic acid (lactic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.1 and 6.9 when arginine 0.5 M and 1.0 M respectively are incorporated into the formulations. 2-Methyl 2-hydroxypropanoic acid (methyllactic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.3, 3.4 and 3.2 when 0.5 M each of arginine, creatinine and 4-aminobutanoic acid respectively are incorporated into the formulations. 2-Hydroxybutane-1,4-dioic acid (malic acid) 1 M aqueous solution has pH 1.8, but the pH of the composition changes to 3.0 when creatinine 0.5 M is incorporated into the formulation.

Ideally, an amphoteric compound should contain both anionic and cationic groups or functional groups capable of behaving both as an acid and a base. Although inorganic amphoteric compounds such as aluminum oxide, aluminum hydroxide and zinc oxide may be utilized, organic amphoteric compounds have been found to be more efficient in formulating therapeutic compositions of the instant invention.

Organic amphoteric and pseudoamphoteric compounds may be classified into three groups, namely (a) amino acid type, (b) imidazoline and lecithin amphoterics and (c) pseudoamphoterics and miscellaneous amphoterics.

(a) Amino acid type amphoterics. Amphoteric compounds of amino acid type include all the amino acids, dipeptides, polypeptides, proteins and the like which contain at least one of the basic groups such as amino, imino, guanido, imidazolino and imidazolyl, and one of the acidic groups such as carboxylic, sulfonic, sulfinic and sulfate.

Glycine is a simple amphoteric compound which contains only one amino group and one carboxylic group. Lysine contains two amino groups and one carboxylic group. Aspartic acid contains one amino group and two carboxylic groups. Arginine contains one amino group, one guanido group and one carboxylic group. Histidine contains one amino group, one imidazolyl group and one carboxylic group. Taurine contains one amino group and one sulfonic group. Cysteine sulfinic acid contains one amino group, one carboxylic group and one sulfinic group. The amino group of an amphoteric compound may also be substituted, such as in betaine which is a glycine N,N,N-trimethyl inner salt.

Glycylglycine is a simple dipeptide which contains one free amino group and one free carboxylic group. Glycylhistidine is also a dipeptide which contains one free amino group, one imidazolyl group and one free carboxylic group.

The representative amphoteric compounds of amino acid type may be listed as follows: Glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline and proline.

The related amino acids include homocysteine, homocystine, homoserine, ornithine; citrulline, creatine, 3-aminopropanoic acid, theanine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, phenylglycine, canavanine, canal ine, 4 -hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β-lysine, 2,4-diaminobutanoic acid, 2,3-diaminoproparoic acid, 2-methylserine, 3-phenylserine and betaine.

Sulfur-containing amino acids include taurine, cysteinesulfinic acid, methionine sulfoxide and methionine sulfone.

The halogen-containing amino acids include 3,5-diiodotyrosine, thyroxine and monoiodotyrosine. The imino type acids include pipecolic acid, 4-aminopipecolic acid and 4-methylproline.

The dipeptides include for example, glycylglycine, carnosine, anserine, ophidine, homocarnosine, β-alanyllysine, β-alanylarginine. The tripeptides include for example, glutathione, ophthalmic acid and norophthalmic acid. Short-chain polypeptides of animal, plant and bacterial origin containing up to 100 amino acid residues include bradykinin and glucagon. The preferred proteins include for example protamines, histones and other lysine and arginine rich proteins.

(b) Imidazoline and lecithin amphoterics. The amphoteric compounds of imidazoline derived type are commercially synthesized from 2-substituted-2-imidazolines obtained by reacting a fatty acid with an aminoethylethanolamine. These amphoterics include cocoamphoglycine, cocoamphopropionate, and cocoamphopropylsulfonate. The amphoteric compounds of lecithin and related type include for example, phosphatidyl ethanolamine, phosphatidyl serine and sphingomyelin.

(c) Pseudoamphoterics and miscellaneous amphoterics. Many pseudoamphoteric compounds are chemically related or derived from true amphoterics. For example, creatinine is derived from creatine. Other pseudoamphoteric compounds may include fatty amide amines such as stearamidoethyl diethylamine, stearamidoethyl diethanolamine and stearamidopropyl dimethylamine. Other pseudoamphoteric related compounds include quaternary ammonium hydroxide and quaternium hydroxide.

In accordance with the present invention, the alpha hydroxyacid, the alpha ketoacids and the related compounds which are incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders may be classified into three groups.

The first group is organic carboxylic acids in which one hydroxyl group is attached to the alpha carbon of the acids. The generic structure of such alpha hydroxyacids may be represented as follows:

(Ra) (Rb) C (OH) COOH

where Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha hydroxyacids may be present as a free acid or lactone form, or in a salt form with an organic base or an inorganic alkali. The alpha hydroxyacids may exist as stereoisomers as D, L, and DL forms when Ra and Rb are not identical.

Typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc. The alpha hydroxyacids of the first group may be divided into (1) alkyl alpha hydroxyacids, (2) aralkyl and aryl alpha hydroxyacids, (3) polyhydroxy alpha hydroxyacids, and (4) polycarboxylic alpha hydroxyacids. The following are representative alpha hydroxyacids in each subgroup.

(1) Alkyl Alpha Hydroxyacids

1. 2-Hydroxyethancic acid (Glycolic acid, hydroxyacetic acid)
   (H) (H) C (OH) COOH
2. 2-Hydroxypropanoic acid (Lactic acid)
   ($CH_3$) (H) C (OH) COOH
3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid)
   ($CH_3$) ($CH_3$) C (OH) COOH
4. 2-Hydroxybutanoic acid
   ($C_2H_5$) (H) C (OH) COOH
5. 2-Hydroxypentanoic acid
   ($C_3H_7$) (H) C (OH) COOH
6. 2-Hydroxyhexanoic acid
   ($C_4H_9$) (H) C (OH) COOH
7. 2-Hydroxyheptanoic acid
   ($C_5H_{11}$) (H) C (OH) COOH
8. 2-Hydroxyoctanoic acid
   ($C_6H_{13}$) (H) C (OH) COOH
9. 2-Hydroxynonanoic acid
   ($C_7H_{15}$) (H) C (OH) COOH
10. 2-Hydroxydecanoic acid
    $C_8H_{17}$) (H) C (OH) COOH
11. 2-Hydroxyundecanoic acid
    ($C_9H_{19}$) (H) C (OH) COOH
12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid)
    ($C_{10}H_{21}$) (H) C (OH) COOH
3. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid)
   ($C_{12}H_{25}$) (H) C (OH) COOH
14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid)
    $C_{14}H_{29}$) (H) C (OH) COOH
15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid)
    ($C_{16}H_{34}$) (H) C (OH) COOH
16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid)
    ($C_{18}H_{37}$) (H) C (OH) COOH

(2) Aralkyl And Aryl Alpha Hydroxyacids

1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid)
   ($C_6H_5$) (H) C (OH) COOH
2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid)
   ($C_6H_5$) ($C_6H_5$) C (OH) COOH
3. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid)
   ($C_6H_5CH_2$) (H) C (OH) COOH
4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid)
   ($C_6H_5$) ($CH_3$) C (OH) COOH
5. 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid (4-Hydroxymandelic acid)
   (HO-$C_6H_4$) (H) C (OH) COOH

2-(4'-Chlorophenyl) 2-hydroxyethanoic acid (4-Chloromandelic acid)
(Cl-$C_6H_4$) (H) C (OH) COOH

7. 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid (3-Hydroxy-4-methoxymandelic acid)
(HO-,$CH_3O$-$C_6H_3$) (H) C (OH) COOH

8. 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid (4-Hydroxy-3-methoxymandelic acid)
(HO-,$CH_3O$-$C_6H_3$) (H) C (OH) COOH

9. 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(2'Hydroxyphenyl) lactic acid]
HO-$C_6H_4$-$CH_2$(H) C (OH) COOH

10. 3-(4'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(4'-Hydroxyphenyl) lactic acid]
HO-$C_6H_4$-$CH_2$ (H) C (OH) COOH

11. 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid (3,4-Dihydroxymandelic acid)
HO-,HO-$C_6H_3$ (H) C (OH) COOH

(3) Polyhydroxy Alpha Hydroxyacids

1. 2,3-Dihydroxypropanoic acid (Glyceric acid)
($HOCH_2$) (H) C (OH) COOH

2. 2,3,4-Trihydroxybutanoic acid ,Isomers; erythronic acid, threonic acid)
$HOCH_2$ (HO)$CH_2$ (H) C (OH) COOH

3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid)
$HOCH_2$ (HO)$CH_2$ (HO)$CH_2$ (H) C (OH) COOH

4. 2,3,4,5,6-Pentahydroxyhexancic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid)
$HOCH_2$ (HO)$CH_2$ (HO)$CH_2$ (HO)$CH_2$ (H) C (OH) COOH

5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.)
$HOCH_2$ (HO)$CH_2$ (HO)$CH_2$ (HO)$CH_2$ (HO)$CH_2$ (H) C (OH) COOH

(4) Polycarboxylic Alpha Hydroxyacids

1. 2-Hydroxypropane-1,3-dioic acid (Tartronic acid)
HOOC (H) C (OH) COOH

2. 2-Hydroxybutane-1,4-dioic acid (Malic acid)
HOOC $CH_2$ (H) C (OH) COOH

3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid)
HOOC (HO)CH (H) C (OH) COOH

4. 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid)
HOOC $CH_2$ C (OH)(COOH) $CH_2$ COOH

5. 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic: acid, mucic acid etc.)
HOOC $(CHOH)_4$ COOH

(5) Lactone Forms

The typical lactone forms are gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, and galactoheptonolactone.

The second group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders, is organic carboxylic acids in which the alpha carbon of the acids is in keto form. The generic structure of such alpha ketoacids may be represented as follows:

(Ra) CO COO(Rb)

wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha ketoacids may be present as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc.

In contrast to alpha hydroxyacids the ester form of alpha ketoacids has been found to be therapeutically effective for cosmetic and dermatologic conditions and disorders. For example, while ethyl lactate has a minimal effect, ethyl pyruvate is therapeutically very effective. Although the real mechanism for such difference is not known we have speculated that the ester form of an alpha ketoacid is chemically and/or biochemically very reactive, and a free acid form of the alpha ketoacid is released in the skin after the topical application.

The representative alpha ketoacids and their esters which may be useful in amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders are listed below:

1. 2-Ketoethanoic acid (Glyoxylic acid)
(H) CO COOH

2. Methyl 2-ketoethanoate
(H) CO $COOCH_3$

3. 2-Ketopropanoic acid (Pyruvic acid)
$CH_3$ CO COOH

4. Methyl 2-ketopropanoate (Methyl pyruvate)
$CH_3$ CO $COOCH_3$

5. Ethyl 2-ketopropanoate (Ethyl pyruvate)
$CH_3$ CO $COOC_2H_5$

6. Propyl 2-ketopropanoate (Propyl pyruvate)
$CH_3$ CO $COOC_3H_7$

7. 2-Phenyl-2-ketoethanoic acid Benzoylformic acid)
$C_6H_5$ CO COOH

8. Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate)
$C_6H_5$ CO $COOCH_3$

9. Ethyl 2 -phenyl-2 -ketoethanoate (Ethyl benzoylformate)
$C_6H_5$ CO $COOC_2H_5$

10. 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid)
$C_6H_5CH_2$ CO COOH

11. Methyl 3-phenyl-2-ketopropanoate (Methyl phenylpyruvate)
$C_6H_5CH_2$ CO $COOCH_3$

12. Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate)
$C_6H_5CH_2$ CO $COOC_2H_5$

13. 2-Ketobutanoic acid
$C_2H_5$ CO COOH

14. 2-Ketopentanoic acid
$C_3H_7$ CO COOH

15. 2-Ketohexanoic acid
$C_4H_9$ CO COOH

16. 2-Ketoheptanoic acid
$C_5H_{11}$ CO COOH

17. 2-Ketooctanoic acid
$C_6H_{13}$ CO COOH

18. 2-Ketododecanoic acid
$C_{10}H_{21}$ CO COOH

19. Methyl 2-ketooctanoate
$C_6H_{13}$ CO $COOCH_3$

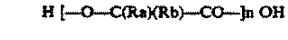
The third group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic and dermatologic conditions and disorders, is chemically related to alpha hydroxyacids or alpha ketoacids, and can be represented by their names instead of the above two generic structures. The third group of compounds include ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

II. Dimeric and Polymeric Forms of Hydroxyacids

When two or more molecules of hydroxycarboxylic acids either identical or non-identical compounds are reacted chemically to each other, dimeric or polymeric compounds will be formed. Such dimeric and polymeric compounds may be classified into three groups, namely (a) acyclic ester, (b) cyclic ester and (c) miscellaneous dimer and polymer.

(a) Acyclic ester. The acyclic ester of a hydroxycarboxylic acid may be a dimer or a polymer. The dimer is formed from two molecules of a hydroxycarboxylic acid by reacting the carboxyl group of one molecule with the hydroxy group of a second molecule. For example, glycolyl glycollate is formed from two molecules of glycolic acid by eliminating one mole of water molecule. Likewise, lactyl lactate is formed from two molecules of lactic acid. When two molecules of different hydroxycarboxylic acids are intermolecularly reacted, a different dimer is formed. For example, glycolyl lactate is formed by reacting the carboxyl group of lactic acid with the hydroxy group of glycolic acid. The polymer is formed in a similar manner but from more than two molecules of a hydroxycarboxylic acid. For example, glycoly glycoly glycollate is formed from three molecules of glycolic acid. Copolymer is formed from two or more than two different kinds of hydroxycarboxylic acids. For example, glycolyl lactyl glycollate is formed from two molecules of glycolic acid and one molecule of lactic acid.

The acyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

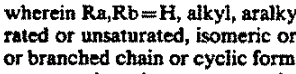


wherein Ra,Rb=H, alkyl, aralkyl ar aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=1 or any numerical number, with a preferred number of up to 200. Ra and Rb in monomer unit 2, 3, 4 and so on may be the same or the different groups from that in monomer unit 1. For example, Ra,Rb=H in monomer unit 1, and Ra=$CH_3$, Rb=H in monomer unit 2 when n=2 is a dimer called lactyl glycollate, because the first monomer is glycollate unit and the second monomer is lactic acid unit. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms. The dimer and polymer of a hydroxycarboxylic acid may be present as a free acid, ester or salt form with organic base or inorganic alkali.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative acyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolyl glycollate (Glycolic acid glycollate)
Ra,Rb=H in units 1 & 2, n=2
2. Lactyl lactate (Lactic acid lactate)
Ra=$CH_3$, Rb=H in units 1&2, n=2
3. Mandelyl mandellate
Ra=$C_6H_5$, Rb=H in units 1 & 2, n=2
4. Atrolactyl atrolactate
Ra=$C_6H_5$, Rb=$CH_3$ in units 1 & 2, n=2
5. Phenyllactyl phenyllactate
Ra=$C_6H_5CH_2$, Rb=H, in units 1 & 2, n=2
6. Benzilyl benzillate
Ra,Rb=$C_6H_5$ in units 1 & 2, n=2
7. Glycolyl lactate
Ra=$CH_3$ in unit 1, Ra=H in unit 2, Rb=H in units 1 & 2, n=2
8. Lactyl glycollate
Ra=H in unit 1, Ra=$CH_3$ in unit 2, Rb=H in units 1 & 2, n=2
9. Glycolyl glycolyl glycollate
Ra,Rb=H in units 1, 2 & 3, n=3
10. Lactyl lactyl lactate
Ra=$CH_3$, Rb=H in units 1, 2 & 3, n=3
11. Lactyl glycolyl lactate
Ra=$CH_3$ in units 1 & 3, Ra=H in unit 2, Rb=H in units 1, 2 & 3, n=3
12. Glycolyl glycolyl glycolyl glycollate
Ra,Rb=H in units 1, 2, 3 & 4, n=4
13. Lactyl lactyl lactyl lactate
Ra=$CH_3$, Rb=H in units 1, 2, 3 & 4, n=4
14. Glycolyl lactyl glycolyl lactyl glycollate
Ra=H in units 1, 3 & 5, Ra=$CH_3$ in units 2 & 4, Rb=H in units 1, 2, 3, 4 & 5, n=5
15. Polyglycolic acid and polylactic acid

(b) Cyclic ester. The cyclic ester of a hydroxycarboxylic acid may also be a dimer or polymer, the most common type however, is a dimer form. The cyclic dimer may be formed from an identical monomer or different monomers. For example, glycolide is formed from two molecules of glycolic acid by removing two molecules of water, and lactide is formed from two molecules of lactic acid in the same manner. The cyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:



wherein Ra,Rb=H, alkyl, aralkyl or aryl group of saturated or unsaturated isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=1 or any numerical number, however with a preferred number of 2. Ra and Rb in units 1, 2, 3 and so on may be the same or the different groups. For example, in glycolide Ra and Rb are H in both units 1 & 2, but in lactoglycolide Ra is H in unit 1, $CH_3$ in unit 2 and Rb is H in both units 1 & 2. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative cyclic esters of hydrox-

ycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolide
   Ra, Rb═H, n=2
2. Lactide
   Ra═$CH_3$, Rb═H in units 1 & 2, n=2
3. Mandelide
   Ra═$C_6H_5$, Rb═H in units 1 & 2, n=2
4. Atrolactide
   Ra═$C_6H_5$, Rb═$CH_3$ in units 1 & 2, n=2
5. Phenyllactide
   Ra═$C_6H_5CH_2$, Rb═H in units 1 & 2, n=2
6. Benzilide
   Ra, Rb═$C_6H_5$in units 1 & 2, n=2
7. Methyllactide
   Ra, Rb═$CH_3$ in units 1 & 2, n=2
8. Lactoglycolide
   Ra═H in unit 1, Ra═$CH_3$ in unit 2 Rb═H in units 1 & 2, n=2
9. Glycolactide
   Ra═$CH_3$ in unit 1, Ra═H in unit 2 Rb═H in units 1 & 2, n=2

(c) Miscellaneous dimer and polymer. This group includes all the dimeric and polymeric forms of hydroxycarboxylic acids, which can not be represented by any one of the above two generic structures, such as those formed from tropic acid, trethocanic acid and aleuritic acid. When a hydroxycarboxylic acid has more than one hydroxy or carboxy group in the molecule a complex polymer may be formed. Such complex polymer may consist of acyclic as well as cyclic structures.

The following hydroxycarboxylic acids have more than one hydroxy groups: glyceric acid, gluconic acid and gluconolactone, galactonic acid and galactonolactone, glucuronic acid and glucuronolactone, ribonic acid and ribonolactone, galacturonic acid and galacturonolactone, ascorbic acid, gulonic acid and gulonolactone, glucoheptonic acid and glucoheptonolactone. These polyhydroxycarboxylic acids can form complex polymers with themselves or with other simple monohydroxymonocarboxylic acids.

The following hydroxycarboxylic acids have more than one carboxyl groups: malic acid, citric acid, citramalic acid, tartronic acid, agaricic acid and isocitric acid. These monohydroxypolycarboxylic acids can also form complex polymers with themselves or with other simple hydroxycartoxylic acids.

The following hydroxycarboxylic acids have more than one hydroxy and more than one carboxyl groups: tartaric acid, mucic acid and saccharic acid. These polyhydroxypolycarboxylic acids can form even more complex polymers with themselves or with other hydroxycarboxylic acids.

## III. Combination Compositions

Any cosmetic and pharmaceutical agents may be incorporated into amphoteric or pseudoamphoteric compositions, or into compositions containing dimeric or polymeric forms of hydroxyacids with or without amphoteric or pseudoamphoteric systems to enhance therapeutic effects of those cosmetic and pharmaceutical agents to improve cosmetic conditions or to alleviate the symptoms of dermatologic disorder. Cosmetic and pharmaceutical agents include those that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic agents; antiemetics; antimotion sickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidryskin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical cardiovascular agents and other dermatologicals.

Some examples of cosmetic and pharmaceutical agents are clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobenzone, erythromycin, tetracycline, clindamycin, meclocycline, hydroquinone, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate and vitamin E acetate.

## IV. Specific Compositions For Skin Disorders

We have discovered that topical formulations or compositions containing specific alpha hydroxyacids or alpha ketoacids, or related compounds are therapeutically very effective for certain skin disorders without utilizing any amphoteric or pseudoamphoteric systems. The alpha hydroxyacids and the related compounds include 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid. The alpha ketoacids and their esters include 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate. The mentioned skin disorders include warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

In general, the concentration of the alpha hydroxyacid, the alpha ketoacid or the related compound used in the composition is a full strength to an intermediate strength, therefore the dispensing and the application require special handling and procedures.

If the alpha hdyroxyacid, or the alpha ketoacid or the related compound at full strength (usually 95–100%) is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the liquid compound with or without a gelling agent is directly dispensed as 0.5 to 1 ml aliquots in small vials.

If the alpha hydroxyacid, or the alpha ketoacid or the related compound at full strength is a solid form at room temperature such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid, the solid compound is first dissolved in a minimal amount of vehicle or vehicle system such as water, or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 g, and the 70% strength solution thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, 0.5 to 3% of for example, hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose or carbomer may be incorporated into the above solution.

To prepare an intermediate strength (usually 20–50%), the alpha hydroxyacid, alpha ketoacid or related compound either a liquid or solid form at room temperature is first dissolved in a vehicle or vehicle system such as water, acetone, ethanol, propylene glycol and butane 1,3-diol. For example, 2-hydroxyethanoic acid or 2-ketopropanoic acid 30 g is dissolved in ethanol 56 g and propylene glycol 14 g, and the 30% strength solution thus obtained is dispensed as 7 to 14 ml aliquots in dropper bottles.

For topical treatment of warts, keratoses, age spots, acne, nail infections, wrinkles or aging related skin changes, patients are advised to apply a small drop of the medication with a toothpick or a fine-caliber, commonly available artist's camel hair brush to affected lesions only and not surrounding skin. Prescribed applications have been 1 to 6 times daily for keratoses and ordinary warts of the hands, fingers, palms, and soles. For age spots, acne, nail infections, wrinkles and aging related skin changes topical applications have been 1 to 2 times daily.

Very often, frequency and duration of applications have been modified according to clinical responses and reactions of the lesions and the patient or responsible family member is instructed accordingly. For example, some clinical manifestations other than pain have been used as a signal to interrupt application. These manifestations include distinct blanching of the lesions or distinct peripheral erythema.

Alternatively, an office procedure may be adapted when a full strength of 2-ketopropanoic acid or 70% 2-hydroxyethanoic acid is used for topical treatment of age spots, keratoses, acne, warts or facial wrinkles.

We have found that the above mentioned alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatments of warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

### Preparation of the Therapeutic Compositions

Amphoteric and pseudoamphoteric compositions of the instant invention may be formulated as solution, gel, lotion, cream, ointment, shampoo, spray, stick, powder or other cosmetic and pharmaceutical preparations.

To prepare an amphoteric or pseudoamphoteric composition in solution form at least one of the aforementioned amphoteric or pseudoamphoteric compounds and in combination at least one of the hydroxyacids or the related compounds are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone or other pharmaceutically acceptable vehicle. The concentration of the amphoteric or pseudoamphoteric compound may range from 0.01 to 10 M, the preferred concentration ranges from 0.1 to 3 M. The concentration of hydroxyacids or the related compounds may range from 0.02 to 12 M, the preferred concentration ranges from 0.2 to 5 M.

In the preparation of an amphoteric or pseudoamphoteric composition in lotion, cream or ointment form, at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are initially dissolved in a solvent such as water, ethanol and/or propylene glycol. The solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment base such as hydrophilic ointment or petrolatum. The concentrations of amphoteric or pseudoamphoteric compounds and hydroxyacids used in the compositions are the same as described above.

Amphoteric and pseudoamphoteric compositions of the instant invention may also be formulated in a gel form. A typical gel composition of the instant invention utilizes at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are dissolved in a mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as methyl cellulose, ethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

Since dimeric and polymeric forms of hydroxyacids are less stable in the presence of water or the like vehicle, cosmetic and pharmaceutical compositions should be prepared as anhydrous formulations. Typical vehicles suitable for such formulations include mineral oil, petrolatum, isopropyl myristate, isopropyl palmitate, diisopropyl adipate, occtyl palmitate, acetone, squalene, squalane, silicone oils, vegetable oils and the like. Therapeutic compositions containing dimeric or polymeric forms of hydroxyacids do not require any incorporation of an amphoteric or pseudoamphoteric compound. The concentration of the dimeric or polymeric form of a hydroxyacid used in the composition may range from 0.1 to 100%, the preferred concentration ranges from to 40%. Therapeutic compositions may be formulated as anhydrous solution, lotion, ointment, spray, powder or the like.

To prepare a combination composition in a pharmaceutically acceptable vehicle, a cosmetic or pharmaceutical agent is incorporated into any one of the above composition by dissolving or mixing the agent into the formulation.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limited. Therefore, any of the aforementioned amphoteric or pseudoamphoteric compounds, hydroxyacids, dimeric or polymeric forms of hydroxyacids may be substituted according to the teachings of this invention in the following examples.

### EXAMPLE 1

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxyethanoic acid (glycolic acid) 7.6 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. An amphoteric composition formulated from 1 M 2-hydroxyethanoic acid and 1 M L-arginine has pH 6.3. The solution has pH 1.9 if no amphoteric compound is incorporated.

### EXAMPLE 2

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-lysine in a cream

form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.3.

## EXAMPLE 3

An amphoteric composition containing M 2-hydroxyethanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of a oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.1.

## EXAMPLE 4

A pseudoamphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.0 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

## EXAMPLE 5

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

## EXAMPLE 6

An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M dipeptide of β-Ala-L-His for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and L-carnosine (β-alanyl-L-histidine) 11.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.5.

## EXAMPLE 7

An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M cycloleucine for cosmetic and dermatologic conditions may be formulated as follows.

2 -Hydroxyethanoic acid 3.8 g and aminocyclopentane-1-carboxylic acid (cycloleucine) 6.5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

## EXAMPLE 8

A pseudoamphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.25 M 1,12-diaminododecane for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and 1.12-diaminododecane 5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

## EXAMPLE 9

An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 5% protamine for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and protamine 5 g, isolated and purified from salmon sperm are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

## EXAMPLE 10

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxypropanoic acid (DL-lactic acid) USP grade 9.0 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-arginine has pH 6.9. The solution has pH 1.9 if no amphoteric compound is incorporated.

## EXAMPLE 11

An amphoteric composition containing M 2-hydroxypropanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.6. An amphoteric composition formulated from M 2-hydroxypropanoic acid and 1 M L-lysine has pH 8.4

## EXAMPLE 12

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0

EXAMPLE 13

A pseudoamphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.3. The composition has pH 4.4 when M instead of b 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 14

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-histidine 15.5 g are dissolved in 35 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated as pH 4.9.

EXAMPLE 15

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and glycylglycine 13.2 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 16

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid (methyllactic acid) 10.4 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. An amphoteric composition formulated from 1 M 2-methyl-2-hydroxypropanoic acid and 1 M L-arginine has pH 6.5. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 17

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and 4-aminobutanoic acid 5.2 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 18

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and glycylglycine 13.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 19

A pseudoamphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4. The composition has pH 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 20

An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic: acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid (mandelic acid) 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 5.0. The composition has pH 2.2 if no amphoteric compound is incorporated.

EXAMPLE 21

An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 25 ml of water. The solution thus obtained is mixed with an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated for pH 4.6.

EXAMPLE 22

A pseudoamphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and creatinine 5.7 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 4.6.

EXAMPLE 23

An amphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M L-citrulline for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-citrulline 8.8 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 24

An amphoteric composition containing 1 M citric acid and 1 M L-arginine for cosmetic conditions and dermatologic disorders may be formulated as follows.

Citric acid 19.2 g is dissolved in water 50 ml and propylene glycol 10 ml. L-Arginine 17.4 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 25

A pseudoamphoteric composition containing 1 M citric acid and 1 M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

Citric acid 19.2 g and creatinine 11.3 g are dissolved in 40 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.7.

EXAMPLE 26

An amphoteric composition containing 1 M malic acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxybutanedioic acid (DL-malic acid) 13.4 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 27

A pseudoamphoteric composition containing 1 M malic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Malic acid 13.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.0. The composition has pH 3.8 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 28

An amphoteric composition containing 1 M tartaric acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

2,3-Dihydroxybutanedioic acid (DL-tartaric acid) 15.9 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.7 if no amphoteric compound is incorporated.

EXAMPLE 29

A pseudoamphoteric composition containing 1 M tartaric acid and 1 ml creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Tartaric acid 15.0 g and creatinine 11.3 g are dissolved in 35 ml of water. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH s3.4.

EXAMPLE 30

An amphoteric composition containing 1 M gluconolactone and 0.5 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and L-arginine 8.7 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. The composition has pH 5.9 when 1 M instead of 0.5 M L-arginine is incorporated into the formulation. If no amphoteric compound is incorporated the pH of the composition is 1.8.

EXAMPLE 31

An amphoteric composition containing 1 M gluconolactone and 0.5 M 4-aminobutanoic acid for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and 4-aminobutanoic acid 5.2 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

Example 32

An amphoteric composition containing 1 M gluconolactone and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and glycylglycine 13.2 g are dissolved in water 50 ml and propylene glycol 5 ml. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1.

Example 33

A pseudoamphoteric composition containing 1 M gluconolactone and 0.5 M creatinine for cosmetic conditions and dermatologic disorders may be formulated as follows.

Gluconolactone 17.8 g and creatinine 5.7 g are dissolved in water 60 ml and propylene glycol 10 ml. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.8 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 34

A pseudoamphoteric composition containing 1 M pyruvic acid and 1 M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

2-Ketopropanoic acid (pyruvic acid) 8.8 g and creatinine 11.3 g are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml.

The amphoteric composition thus formulated has pH 3.4.

EXAMPLE 35

An amphoteric composition containing 0.5 M benzilic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2,2-Diphenyl 2-hydroxyethanoic acid (benzilic acid) 11.4 g and L-lysine 7.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9. The composition has pH 2.7 if no amphoteric compound is incorporated.

EXAMPLE 36

An amphoteric composition containing 0.5 M benzilic acid and 0.5 M L-histidine for cosmetic and dermatologic conditions may be formulated as follows.

Benzilic acid 11.4 g and L-histidine 7.8 g are dissolved in water 40 ml and propylene glycol 20 ml. Ethyl cellulose 2 g is added with stirring, and sufficient amount of ethanol is added to make a total volume of the gel to 100 ml. The amphoteric gel composition thus formulated has pH 5.0.

EXAMPLE 37

A pseudoamphoteric composition containing 0.5 M benzilic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

Benzilic acid 11.4 and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. Sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9.

EXAMPLE 38

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.05% betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Betamethasone dipropionate 1% in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 39

A pseudoamphoteric composition containing in combination 0.5 m 2-hydroxyethanoic acid and 0.05% clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1% in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 40

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.1% triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 41

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.2% 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol: water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 42

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.05% betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of a oil-in-water emulsion. Betamethasone dipropionate 1% in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 43

A pseudoamphoteric composition containing in combination 0.5 M hydroxypropanoic acid and 0.05% clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1% in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 44

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.1% triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 45

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.2% 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol:water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 46

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% clotrimazole in a cream form for athlete's foot and other fungal infections may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, clotimazole 2 g and creatinine 5.7 g are dissolved in water 20 ml and propylene glycol 5 ml, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 47

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% erythromycin in solution form for acne may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, erythromycin 2 g and creatinine 5.7 g are dissolved in water 25 ml, ethanol 40 ml and propylene glycol 15 ml. More water is then added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 48

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 1% ketoconazole in a cream form for fungal infections may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, ketoconazole 1 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 49

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 2% clotrimazole in a cream form for fungal infections may be formulated as follows.

2-Hydroxypropanoic acid 3.8 g, clotrimazole 2 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

EXAMPLE 50

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% tetracycline in a gel form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, tetracycline 2 g, creatinine 5.7 g, xantham gum 0.2 g, carbomer-941 1 g, propylene glycol 5 ml, ethanol 20 ml and enough amount of water are homogenized to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated for acne and oily skin has pH 4.2.

EXAMPLE 51

An amphoteric composition containing 0.2 M aleuritic acid and 0.1 M L-lysine in a solution form for cosmetic and dermatologic conditions may be formulated as follows.

Aleuritic acid 6.1 g and L-lysine 1.5 g are dissolved in sufficient amount of a solution from ethanol:propylene glycol 80:20 to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 6.4.

EXAMPLE 52

A typical composition containing a dimeric form of alpha hydroxyacid in solution for acne, dandruff, and as a skin cleanser may be formulated as follows.

Glycolide powder 1.0 g is dissolved in ethanol 89 ml and propylene glycol 10 ml. The composition thus formulated has pH 4.0, and contains 1% active ingredient.

EXAMPLE 53

A typical composition containing a dimeric form of alpha hdyroxyacid in ointment for dry skin, psoriasis, eczema, pruritus, wrinkles and other skin changes associated with aging may be formulated as follows.

Glycolide powder 2.0 g is mixed uniformly with petrolatum 66 g and mineral oil 32 g. The composition thus formulated contains 2% active ingredient.

EXAMPLE 54

A typical composition containing a full strength or a high concentration of an alpha hydroxyacid, alpha ketoacid or closely related compound for topical treatments of warts, keratoses, acne, age spots, nail infections, wrinkles and aging related skin changes may be prepared as follows.

If the alpha hydroxyacid, alpha ketoacid or closely related compound at full strength is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the compound is directly dispensed as 0.5 to 1 ml aliquots in small vials. If the compound is a solid form at room temperature such as 2-hydroxyethanoic acid and 2-methyl 2-hydroxypropanoic acid, it is first dissolved in minimal amount of an appropriate solvent or solvent system such as water or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 ml, and the 70% strength 2-hydroxyethanoic acid thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, methyl cellulose or hydroxyethyl cellulose 1 g may be added to the above solution.

EXAMPLE 55

A typical composition containing an intermediate strength of an alpha hydroxyacid, alpha ketoacid or closely related compound for topical treatment of warts, keratoses, acne, nail infections, age spots, wrinkles and aging related skin changes may be prepared as follows.

2-Hydroxyethanoic acid or 2-ketopropanoic acid 40 g is dissolved in ethanol 54 g and propylene glycol 6 g,

and the 40% strength solution thus obtained is dispensed as 5 to 10 ml aliquots in dropper bottles.

## TEST RESULTS

In order to determine whether amphoteric and pseudoamphoteric compositions of the instant invention were therapeutically effective for various cosmetic conditions and dermatologic disorders, a total of more than 90 volunteers and patients participated in these studies. Some participating subjects were given two preparations; an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound, and a vehicle placebo. Others were given multiple preparations containing a known pharmaceutical agent such as a corticosteroid with or without incorporation of an amphoteric or pseudoamphoteric composition consisting of an alpha hydroxyacid or the related compound of the instant invention. The amphoteric and pseudoamphoteric compositions were formulated according to the Examples described in the previous section.

### Common dry skin.

Human subjects having ordinary dry skin or with moderate degrees of dry skin as evidenced by dryness, flaking and cracking of the skin were instructed to apply topically the lotion, cream or ointment containing an alpha hydroxyacid or the related compound in amphoteric or pseudoamphoteric composition, on the affected area of the skin. Topical application, two to three times daily, was continued for two to four weeks.

In all the 28 subjects tested, the feeling of the skin dryness disappeared within a week of topical application. The rough and cracked skin became less pronounced and the skin appeared normal and felt smooth after several days of topical treatment. The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective when incorporated into the amphoteric or pseudoamphoteric compositions for dry skin are as follows:

2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), 2-methyl-2-hydroxypropanoic acid (methyllactic acid), phenyl 2-hydroxyethanoic acid (mandelic acid), phenyl 2-methyl-2-hydroxyethanoic acid (atrolactic acid), 3-phenyl-2-hydroxypropanoic acid (phenyllactic acid), diphenyl 2-hydroxyethanoic acid (benzilic acid), gluconolactone, tartaric acid, citric acid, saccharic acid, malic acid, tropic acid, glucuronic acid, galacturonic acid, gluconic acid, 3-hydroxybutanoic acid, quinic acid, ribonolactone, glucuronolactone, galactonolactone, pyruvic acid, methyl pyruvate, ethyl pyruvate, phenylpyruvic acid, benzoylformic acid and methyl benzoylformate.

The ordinary dry skin conditions, once restored to normal appearing skin, remained improved for some time until causes of dry skin, such as low humidity, cold weather, excessive contact pressure, detergents, soaps, solvents, chemicals, etc., again caused recurrence of the dry skin condition. On continued use it was also found that twice daily topical application of an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound of the instant invention prevented the development of new dry skin lesions.

### 2. Severe dry skin.

In severe dry skin, the skin lesions are different from the ordinary dry skin. A main cause of severe dry skin is inherited genetic defects of the skin. The involved skin is hyperplastic, fissured and has thick adherent scales. The degree of thickening is such that lesions are palpably and visually elevated. The thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These two attributes of thickness and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows:

| | DEGREE OF IMPROVEMENT | | | | |
|---|---|---|---|---|---|
| | None (0) | Mild (1+) | Moderate (2+) | Substantial (3+) | Complete (4+) |
| Thickness | Highly elevated | Detectable reduction | Readily apparent reduction | Barely elevated | Normal thickness |
| Texture | Visibly rough | Palpably rough | Uneven but not rough | Slightly uneven | Visibly and palpably smooth |

By means of such parameters, degrees of change in lesions can be numerically recorded and comparisons made of one treated site to another.

In order to evaluate the amphoteric and pseudoamphoteric compositions of the instant invention, a total of 6 patients having severe dry skin conditions were treated with the compositions containing an alpha hydroxyacid or the related compound.

Tested areas were of a size convenient for topical applications, i.e., circles 5 cm in diameter demarcated with a plastic ring of that size inked on a stamp pad. The medicinal lotions or creams were topically applied by the patient in an amount sufficient to cover the treatment sites. Applications were made three times daily and without occlusive dressings. Applications were discontinued at any time when resolutions of the lesion on the treatment area was clinically judged to be complete.

The test results of amphoteric and pseudoamphoteric compositions containing the following alpha hydroxyacids or the related compounds on patients with severe dry skin are summarized as follows:

4+Effectiveness; glycolic acid, lactic acid, methyllactic acid, mandelic acid, tropic acid, atrolactic acid and pyruvic acid.

3+Effectiveness; benzilic acid, gluconolactone, malic acid, tartaric acid, citric acid, saccharic acid, methyl pyruvate, ethyl pyruvate, phenyllactic acid, phenylpyruvic acid, glucuronic acid and 3-hydroxybutanoic acid.

2+Effectiveness; mucic acid, ribonolactone, 2-hydroxydodecanoic acid, quinic acid, benzoylformic acid and methyl benzoylformate.

### 3. Psoriasis.

The involved skin in psoriasis is hyperplastic (thickened), erythematous (red or inflamed), and has thick adherent scales. The degree of thickening is such that lesions are elevated up to 1 mm above the surface of adjacent normal skin; erythema is usually an intense red; the thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These three attributes of thickness, color and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows.

| | DEGREE OF IMPROVEMENT | | | | |
|---|---|---|---|---|---|
| | None (0) | Mild (1+) | Moderate (2+) | Substantial (3+) | Complete (4+) |
| THICKNESS | Highly elevated | Detectable reduction | Readily apparent reduction | Barely elevated | Normal thickness |
| TEXTURE | Visibly rough | Palpably rough | Uneven but not rough | Slightly uneven | Visibly and palpably smooth |
| COLOR | Intense Red | Red | Dark Pink | Light Pink | Normal Skin Color |

By means of such parameters, degree of improvement in psoriatic lesions can be numerically recorded and comparisons made of one treated site to another.

Patients having psoriasis participated in this study. Amphoteric and pseudoamphoteric compositions containing both an alpha hdyroxyacid or the related compound and a corticosteroid were prepared according to the Examples. Compositions containing only a corticosteroid were also prepared and included in the comparison test. Test areas were kept to minimal size convenient for topical application, i.e., circles approximately 4 cm in diameter. The medicinal compositions were topically applied by the patient in an amount (usually about 0.1 milliliter) sufficient to cover the test site. Applications were made two to three times daily and without occlusive dressings. Test periods usually lasted for two to four weeks. The test results on patients having psoriasis are summarized on the following table.

| Topical Effects on Psoriasis of Antipsoriatic Compositions | |
|---|---|
| Compositions* | Therapeutic Effectiveness |
| Hydrocortisone 2.5% alone | 1+ |
| With lactic acid | 2+ |
| With glycolic acid | 2+ |
| With ethyl pyruvate | 2+ |
| With methyl pyruvate | 2+ |
| With benzilic acid | 2+ |
| With pyruvic acid | 2+ |
| With methyllactic acid | 2+ |
| Hydrocortisone 17-valerate 0.2% alone | 2+ |
| With lactic acid | 3+ |
| With glycolic acid | 3+ |
| With benzilic acid | 3+ |
| With ethyl pyruvate | 3+ |
| With methyl pyruvate | 3+ |
| With gluconolactone | 3+ |
| With pyruvic acid | 3+ |
| Betamethasone dipropionate 0.05% alone | 3+ |
| With lactic acid | 4+ |
| With glycolic acid | 4+ |
| With ethyl pyruvate | 4+ |
| With methyl pyruvate | 4+ |
| With mandelic acid | 4+ |
| With benzilic acid | 4+ |
| Clobetasol propionate 0.05% alone | 3+ |
| With lactic acid | 4+ |
| With glycolic acid | 4+ |
| With ethyl pyruvate | 4+ |
| With methyl pyruvate | 4+ |
| With methyllactic acid | 4+ |
| With mandelic acid | 4+ |
| With tropic acid | 4+ |
| With benzilic acid | 4+ |

*Except the "alone" preparations, all others were amphoteric or pseudoamphoteric compositions containing 0.2 to 2M alpha hydroxyacids or related compounds.

We have also found that an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound in combination with an antimetabolite agent such as 5-fluorouracil with or without additional incorporation of a corticosteroid is therapeutically effective for topical treatment of psoriasis.

4. Eczema.

In a topical treatment of eczema patients, hydrocortisone alone at 2.5% or hydrocortisone 17-valerate alone at 0.2% would achieve only 2+improvement, and betamethasone dipropionate or clobetasol propionate alone at 0.05% would achieve only a 3+improvement on all the eczema patients tested. Test results of amphoteric and pseudoamphoteric compositions containing both a corticosteroid and one of the following alpha hydroxyacids or the related compounds are shown as follows:

3+Effectiveness; hydrocortisone 2.5% or hydrocortisone 17-valerate 0.2% plus lactic acid, glycolic acid, mandelic acid, ethyl pyruvate, gluconolactone, benzilic acid or ribonolactone.

4+Effectiveness; betamethasone dipropionate or clobetasol propionate 0.05% plus lactic acid, glycolic acid, mandelic acid, ethyl pyruvate, methyl pyruvate, benzilic acid, gluconolactone, citric acid, tartaric acid or methyllactic acid.

5 Oily Skin and Skin Cleanse.

Human subjects having oily skin or blemished skin as well as acne patients having extremely oily skin participated in this study. Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds were formulated in solution or gel form.

Each participating subject received a solution or a gel preparation containing an alpha hydroxyacid or a related compound in an amphoteric or pseudoamphoteric composition. The participating subjects were instructed to apply topically the solution or gel medication on the affected areas of forehead or other part of the face. Three times daily applications were continued for 2 to 6 weeks.

The degree of improvement of oily skin as well as the rate of improvement of acne lesions were clinically evaluated. Most participants reported that oiliness of skin disappeared within one to two weeks of topical administration, and the skin so treated became smooth and soft. Many participating subjects preferred gel preparations than solution compositions. It was found that all the participants showed substantial improvements on oily skin and acne lesions by six weeks of topical administration of amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds of the instant invention.

Those alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for oily skin and as skin cleansers include: benzilic acid, glycolic acid, lactic acid, methyllactic acid, mandelic acid, pyruvic acid, ethyl pyruvate, methyl pyruvate, tropic acid, malic acid, gluconolactone, 3-hydroxybutanoic acid, glycolide and polyglycolic acid. As a skin cleanser for oily skin or acne-prone skin, the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound may also be incorporated with other dermatologic agents. For example, an amphoteric gel composition may consist of both an alpha hydroxyacid and erythromycin or tetracycline.

6. Acne

Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds of the instant invention in a solution or gel form were provided to patients having comedongenic and/or papulopustular lesions of acne. Each participating patient was instructed to apply topically the composition on the involved areas of the skin such as forehead, face and chest. Three times daily administration was continued for 6 to 12 weeks.

The degree and rate of improvement on acne lesions were clinically evaluated. It was found that acne lesions consisting mainly of comedones improved substantially after 6 to 8 weeks of topical administration with the amphoteric or the pseudoamphoteric composition containing an alpha hydroxyacid or the related compound. The time for complete clearing of comedongenic acne treated with the amphoteric or pseudoamphoteric composition of the instant invention varied from 6 to 12 weeks.

As a topical treatment for papulopustular and/or pustular acne the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound may incorporate in addition an antiacne agent. The antiacne agents include antibiotics such as erythromycin, tetracycline, clindamycin, meclocycline and minocycline, and retinoids such as retinoic acid. Such combination compositions have been found to be therapeutically more effective for topical treatment of severe acne.

7. Age Spots

Many small and large discolored lesions, commonly called age spots on the face and the back of the hands are benign keratoses, if they are not variants of actinic keratoses. Very few of such age spots are true lentigines, therefore alpha hydroxyacids and the related compounds may be effective in eradicating most age spots without concurrent use of skin bleaching agents such as hydroquinone and monobenzone. However, additional beneficial effects have been found when a skin bleaching agent such as hydroquinone or monobenzone is also incorporated into the compositions of the instant invention for age spots involving pigmented lesions.

Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds, with or without incorporation of hydroquinone were provided to volunteer subjects and patients having age spot keratoses, melasma, lentigines and/or other pigmented lesions. Each participating subject received two products, i.e., with or without the addition of 2% hydroquinone to the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound.

The volunteer subjects and patients were instructed to apply topically one medication on one side of the body such as left side of the face or on the back of the left hand, and the other medication on the other side of the body such as on right side of the face or on the back of the right hand. Specific instructions were given to the participating subjects that the medications were applied three times daily to the lesions of age spot keratoses, melasmas, lentigines and/or other pigmented lesions. Clinical photos were taken of participating subjects before the initiation of the topical treatment and every 4 weeks during the course of treatment.

At the end of 4 to 8 weeks, improvement of age spot keratoses was clinically discernible. After 4 to 6 months of topical treatment, substantial improvement of age spot keratoses occurred in the majority of subjects tested. Complete eradication of age spot keratoses occurred after 6 to 9 months of topical administration with the amphoteric or pseudoamphoteric compositions of the instant inventions.

Amphoteric or pseudoamphoteric compositions containing both an alpha hydroxyacid or the related compound and hydroquinone were judged to be more effective in eradicating pigmented age spots, melasma, lentigines and other pigmented lesions.

The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for age spots with or without combination with hydroquinone include glycolic acid, lactic acid, methyllactic acid, mandelic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, benzilic acid, gluconolactone, malic acid, tartaric acid, citric acid and tropic acid. For flat or slightly elevated seborrheic keratoses on the face and/or the back of the body, amphoteric or pseudoamphoteric compositions containing higher concentrations of alpha hydroxyacids or the related compounds have been found to be effective in eradicating such lesions.

Actinic keratoses may be successfully treated with amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds in combination with an antimetabolite agent such as 5-fluorouracil.

8. Warts

Eradications of common warts by topical application of amphoteric or pseudoamphoteric compositions require higher than usual concentrations of alpha hydroxyacids or the related compounds in the formulations. The amphoteric or pseudoamphoteric compositions were formulated as a liquid or light gel form, and dispensed usually as 0.5–1 ml aliquots in small vials.

Topical applications were made discreetly to wart lesions by adult patients or by responsible adult family members. For ordinary usual warts of hands, fingers, palms and soles topical applications were made 2 to 4 times daily, and were continued for 2 to 6 weeks. Generally, the overlying stratum corneum of the wart lesion change in appearance after several weeks topical application of the composition. In most cases, the wart lesion simply fell off. The skin then healed normally without forming any scars.

We have also found that when a dermatologic agent such as 5-fluorouracil is incorporated into the amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds, the medications have been very effective for topical treatment of warts without using higher concentrations of alpha hydroxyacids or the related compounds.

The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for topical treatment of warts with or without incorporation of 5-fluorouracil include glycolic acid, lactic acid, pyruvic acid, ethyl pyruvate, methyl pyruvate and mandelic acid.

Topical formulations and compositions containing specific alpha hydroxyacids, alpha ketoacids or the related compounds at full strengths or high to intermediate concentrations prepared according to Examples 54 and 55, without utilizing amphoteric or pseudoamphoteric systems, have also been tested for ordinary

warts of the hands, fingers, palms and soles. Participating patients have been advised to apply a small drop of the medication with a toothpick or a fine caliber brush to the center of a wart lesion only. Prescribed applications have been 3 to 6 times daily, and are continued until the patient feels pain.

For the more rough-surfaced wart, the duration of application has been as short as one or a few days. For lesions with more compact, less permeable stratum corneum, the time to experience pain has been longer. Frequency and duration of applications have been modified according to other clinical responses and reactions of lesions, and the patient or responsible family member is instructed accordingly.

For example, some clinical manifestations other than pain have also been used as a signal to interrupt application. These manifestations have included distinct blanching cf the lesions or distinct peripheral erythema. Very often, discomfort is the usual signal of clinical reactions.

Generally, the overlying stratum corneum of the wart lesions became loose, and the whole wart lesion simply fell off. The skin then healed normally without forming any scars.

### 9. Athlete's Foot and Nail Infections

Amphoteric and pseudoamphoteric compositions containing both an antifungal agent and one of the alpha hydroxyacids or the related compounds were provided to patients having frequent recurrence of fungal infections involving the foot. The antifungal agents include clotrimazole, miconazole, ketoconazole and griseofulvin. When both feet but not toe nails were involved in the infection, the patients were instructed to apply topically the compositions of the instant invention on the left foot, and a brand-name antifungal product on the right foot. Three times daily applications were continued for one to four weeks. The degree and rate of improvement on skin lesions were clinically evaluated, and comparison was made one side of the body against the other. It was found that the skin lesions improved much faster with the amphoteric or pseudoamphoteric compositions containing both the antifungal agent and the alpha hydroxyacid or the related compound. The alpha hydroxyacids or the related compounds seemed to enhance the efficacies of the antifungal agents, and also to eliminate the discomforts such as itching, tingling, burning and irritation due to fungal infections. When toe nails were not involved the infected skin generally healed within one to two weeks from topical application of the amphoteric or pseudoamphoteric composition containing both an antifungal agent and an alpha hydroxyacid or the related compound.

Fungal infections of the nails are very difficult to treat, because antifungal products to date are not therapeutically effective for topical treatment of nails. One of the reasons is that most antifungal drugs have not been formulated as bioavailable forms in the commercial products. When tow nails were involved in the infections, patients were provided with amphoteric or pseudoamphoteric compositions containing in combination an antifungal agent and an alpha hydroxyacid or an alpha ketoacid at higher concentrations ranging from 20 to 99%, dispensed as 1–2 ml aliquots in small vials. The patients were instructed to apply topically the compositions discreetly to the infected nail surface by means of a fine caliber paint brush. the technique was the same as for application of nail polish, that is careful avoidance of contact with lateral nail folds or any peri-ungual skin. Once or twice daily applications were continued for 2 to 8 weeks.

As mentioned above, while brand-name antifungal products are usually not effective against fungus infections within or underneath the nail, it was found that the amphoteric or pseudoamphoteric compositions containing an antifungal agent and an alpha hydroxyacid or alpha ketoacid were therapeutically effective in eradicating fungal infections of the nails. Such treatment may cause in some instances the treated nail plate to become loose and eventually fell off from the nail bed. This happened quite naturally without any feeling of pain nor bleeding, and the skin lesion healed quickly with normal growth of a new nail.

### 10. Wrinkles

Wrinkles of skin may be due to natural aging and/or sun damage. Most fine wrinkles on the face are due to natural or innate aging, while coarse wrinkles on the face are the consequence of actinic or sun damage. Although the real mechanism of wrinkles formation in the skin is still unknown, it has been shown that visible fine wrinkles are due to diminution in the number and diameter of elastic fibers in the papillary dermis, and also due to atrophy of dermis as well as reduction in subcutaneous adipose tissue. Histopathology and electron microscopy studies indicate that coarse wrinkles are due to excessive deposition of abnormal elastic materials in the upper dermis and thickening of the skin. At present there are no commercial products which have been found to be therapeutically effective for topical eradication of wrinkles, although retinoic acid (tretinoin) has been shown to be beneficial for sun damaged skin.

In order to determine whether the amphoteric or pseudoamphoteric composition containing the alpha hydroxyacids, alpha ketoacids or the related compounds are therapeutically effective for wrinkles, patients and volunteer subjects participated in this study. The participants were instructed to apply the formulations of the instant invention twice daily on areas of facial wrinkles for 4 to 12 months. All participants were told to avoid sun exposure, and to use sunscreen products if exposure to sunlight was unavoidable. Photographs of each side of the face for each participant were taken at the beginning of the study and repeated at one to three-month intervals. The participants were asked not to wear any facial make-up at the time of each office visit. Standardized photographic conditions were used including the use of same lot of photographic: film, the same light source at two feet from the face, aimed at a locus on the frontal aspect of each cheek. Each time photographs were taken with camera aimed perpendicular to the cheek. At the end of study twenty two participants had been entered into the study for at least four months. Clinical evaluations and review of photographs have revealed substantial reductions in facial wrinkles of the temporal region and cheek area on at least one side of the face in eighteen cases. Degree of improvement and reduction in wrinkles has been evaluated and determined to be mild to moderate in six participants but very substantial in twelve participants.

The alpha hydroxyacids, alpha ketoacids and other related compounds including their lactone forms which may be incorporated into the amphoteric and pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders such as dry skin, acne, age spots,

keratoses, warts and skin wrinkles or in combination with other dermatologic agents to enhance therapeutic effects include the following:

(1) Alkyl Alpha Hydroxyacids

2-Hydroxyethanoic acid (Glycolic acid), 2-Hydroxypropanoic acid (Lactic acid), 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid), 2-Hydroxybutanoic acid, 2-Hydroxypentanoic acid, 2-Hydroxyhexanoic acid, 2-Hydroxyheptanoic acid, 2-Hydroxyoctanoic acid, 2-Hydroxynonanoic acid, 2-Hydroxydecanoic acid, 2-Hydroxyundecanoic acid, 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid), 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid), 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid), 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid), 2- Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid).

(2) Aralkyl And Aryl Alpha Hydroxyacids

2-Phenyl 2-hydroxyethanoic acid (Mandelic acid), 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid), 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid), 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Clorophenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-Hydroxyphenyl) Hydroxyphenyl) 2-hydroxypropanoic acid, 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid.

(3) Polyhydroxy Alpha Hydroxyacids

2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid), 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid), 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; aldonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid),. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid, etc.)

(4) Polycarboxylic Alpha Hydroxyacids

2-Hydroxypropane-1,3-dioic acid (Tartronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid), 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid, etc.)

(5) Alpha Hydroxyacid Related Compounds

Ascorbic acid, quinic acid, isocitric acid, tropic acid, 3-chlorolactic acid, trethocanic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid and aleuritic acid.

(6) Alpha Ketoacids And Related Compounds

2-Ketoethanoic acid (Glyoxylic acid), Methyl 2-ketoethanoate, 2-Ketopropanoic acid (Pyruvic acid), Methyl 2-ketopropanoate (Methyl pyruvate), Ethyl, 2-ketopropanoate (Ethyl pyruvate), Propyl 2-ketopropanoate (Propyl pyruvate), 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid), Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate), Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate), 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), Methyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate), 2-Ketobutanoic acid, 2-Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketoheptanoic acid, 2-Ketooctanoic acid, 2-Ketododecanoic acid, Methyl 2-ketooctanoate

The amphoteric and pseudoamphoteric compounds which may be incorporated into the compositions of the instant invention for cosmetic and dermatologic conditions include amino acids, peptides, polypeptides, proteins and the like compounds such as creatinine and creatine.

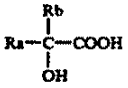
The dimeric and polymeric forms of alpha hydroxyacids and the related comopounds which may be incorporated into the compositions of the instant invention include a cyclic esters and cyclic ester; for example, glycolyl glycollate, lactyl lactate, glycolide, lactide, polyglycolic acid and polylactic acid.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims and all changes which come within the meaning and equivalency of the claims are therefore intended to be embraced therein.

I claim:

1. A composition comprising in combination an amphoteric or pseudoamphoteric agent and an alpha hydroxyacid, an alpha ketoacid or a related compound present in a therapeutically effective amount in a pharmaceutically acceptable vehicle for topical treatment of cosmetic conditions or dermatologic disorders, said amphoteric or pseudoamphoteric agent being at least one member selected from the group consisting of amino acids, dipeptides, polypeptides, proteins, creatine, aminoaldonic acid, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, creatinine, stearamidoethyl diethylamine, stearamidoethyl diethanolamine, stearaminopropyl dimethylamine, cocoamphoglycino cocoamphopropionate, cocoampho, propylsulfonate, phosphatidyl, ethanol-amine, phosphatidylserine and sphingomyelin, and zine oxide and aluminum oxide, said amphoteric or pseudoamphoteric agent being present in a concentration effective to form an amphoteric or pseudoamphoteric system with said alpha hydroxyacid, alpha ketoacid or related compound;

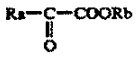
said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid having the following chemical structure:



wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having

1 to 9 carbon atoms, said alpha hydroxyacid existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers, and D, L, and DL forms when Ra and Rb are not identical;

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:



wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali; and

said related compound being at least one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

2. The composition of claim 1 wherein said amphoteric or pseudoamphoteric agent is at least one member selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, aminoaldonic acids, aminouronic acids, aminoaldaric acids, lauryl aminopropylglycine, neuraminic acid, desulfated heparing, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, creatinine, 3-amniopropanoic acid, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, theanine, phenylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β-lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, 2-methylserine, 3-phenylserine, beataine, taurine, cysteinesulfinic acid, methionine sulfoxide, methionine sulfone, 3,5-diiodotyrosine, thyroxine, monoiodotyrosine, pipecolic acid, 4-aminopipecolic acid, 4-methylproline, glycylglycine, carnosine, anserine, ophidine, homocarnosine, β-alanyllysine, β-alanylarginine, glutathione, ophthalmic acid, norophthalmic acid, bradykinin, glucagon, protamines, histones, cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyl ethanolamine, phosphatidyl serine, sphingomyeline, stearamidoethyl diethylamine, stearamidoethyl diethanolamine, stearamidopropyl dimethylamine, quaternary ammonium hydroxide, quaternium hydorxide, aluminum oxide or zinc oxide.

3. The composition of claim 1 wherein said alkyl alpha hydroxyacid is at least one member selected from the group consisting of 2-Hydroxyethanoic acid (Glycolic acid), 2-Hydroxypropanoic acid (Lactic acid), 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid), 2-Hydroxybutanoic acid, 2-Hydroxypentanoic acid, 2-Hydroxyhexanoic acid, 2-Hydroxyheptanoic acid, 2-Hydroxyoctanoic acid, 2-Hydroxynonanoic acid, 2-Hydroxydecanoic acid, 2-Hydroxyundecanoic acid, 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid), 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid), 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid), 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid), 2- Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid).

4. The composition of claim 1 wherein said aralkyl and aryl alpha hydroxyacid is selected from the group consisting of 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid), 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid), 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid), 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Chlorophenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-Hydroxyphenyl) 2-hyroxypropanoic acid, or 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid.

5. The composition of claim 1 wherein said polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid is at least one member selected from the group consisting of 2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid), 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid), 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid galactonic acid, talonic acid), 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.), 2-Hydroxypropane-1,3-dioic acid (Targtronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid), 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid, etc.), or lactone forms (gluconolactone, galactonolaotone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllact one, glucoheptonolactone, mannonolactone, galactoheptonolactone, etc.).

6. The composition of claim 1 wherein said alpha ketoacid and its ester is at least one member selected from the group consisting of 2-Ketoethanoic acid (Glyoxylic acid), Methyl 2-ketoethanoate, 2-Ketopropanoic acid (Pyruvic acid), Methyl 2-ketopropanoate (Methyl pyruvate), Ethyl 2-ketopropanoate (Ethyl pyruvate), Propyl 2-ketopropanoate (Propyl pyruvate), 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid), Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate), Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate), 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), Methyl 3-phenyl-2- ketopropanoate (Methyl phenylpyruvate), Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate), 2-Ketobutanoic acid, 2-Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketopheptanoic acid, 2-Ketooctanoic acid, 2-Ketododecanoic acid, or Methyl 2-ketooctanoate.

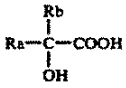
7. The composition of claim 1 wherein said cosmetic conditions, and dermatologic disorders include dry sin, zerosis, ichthyosis, dandruff, brownish spots, keratoses, melasma, lentigines, age spots, liver spots, pigmented spots, wrinkles, blemishes, skin lines, oily skin, acne,

warts, eczema, pruritic skin, psoriasis, inflammatory dermatoses, disturbed deratinization, skin changes associated with aging, nail or skin requiring cleansers, conditioning or treatment, and hair or scalp requiring shampooing or conditioning.

**8.** A therapeutic composition for topical treatment of warts, nail infections, age spots, wrinkles and aging related skin changes comprising an alpha hydroxyacids, alpha ketoacids or related compounds said alpha hydroxyacids, alpha ketoacids or related compounds being selected from the group consisting of 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate present as a free acid lactone, ester or in salt form with an organic base or an inorganic alkali in a pharmaceutically acceptable vehicle.

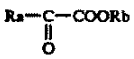
**9.** Method of topical treatment for warts, nail infections, age spots, wrinkles and aging related skin changes comprising topically applying a therapeutically effective amount of alpha hydroxyacids, alpha ketoacids, or related compounds in a pharmaceutically acceptable vehicle for topical treatment;

said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid represented by the following chemical structure:



wherein Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers as D, L, and DL forms when Ra and Rb are not identical;

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:

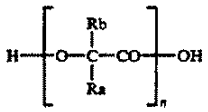


wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali; and

said related compound being at least one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

**10.** The method of claim **9** wherein said alpha hydroxyacids, alpha ketoacids or related compound is selected from the group consisting of 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate or ethyl 2-ketopropanoate.

**11.** A therapeutic composition for topical treatment of cosmetic conditions or dermatologic disorders, comprising dimeric or polymeric forms of hydroxyacids represented by the following chemical structure:

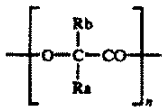


wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and n=2 or any number up to 200; Ra and Rb in monomer unit 2 through 200 may be the same or the different groups from that in monomer unit 1; the hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical of lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 9 carbon atoms, or cyclic form having 5 or 6 ring members, and the dimeric and polymeric forms of hydroxyacids being present as a free acid, ester or in a salt form with an organic base or inorganic alkali in a pharmaceutically acceptable vehicle.

**12.** The composition of claim **11** wherein said dimeric or polymeric forms of hydroxyacids are selected from the group consisting of glycolyl glycollate, lactyl lactate, mandelyl mandellate, atrolactyl atrolactate, phenyllactyl phenyllactate, benzilyl benzillate, glycolyl lactate, lactyl glycollate, triglycolic acid, trilactic acid, polyglycolic acid or polylactic acid.

**13.** The composition of claim **11** further comprising a cosmetic or pharmaceutic agent incorporated as a combination ingredient in said composition.

**14.** A therapeutic composition for topical treatment of cosmetic conditions or dermatologic disorders, comprising dimeric or polymeric forms of hydroxyacids represented by the following chemical structure:



wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and n=2 or any number up to 200, and Ra or Rb may be identical or not identical in the monomer units in a pharmaceutically acceptable vehicle.

15. The composition of claim 14 wherein said dimeric or polymeric forms of hydroxyacids are selected from the group consisting of glycolide, lactide, mandelide, atrolactide, phenyllactide, benzilide, methyllactide, lactoglycolide or glycolactide.

16. The composition of claim 14 further comprising a cosmetic or pharmaceutic agent incorporated as a combination ingredients in said composition.

17. The method of claim 9 wherein said alkyl alpha hydroxyacid is at least one member selected from the group consisting of 2-Hydroxyethanoic acid (Glycolic acid), 2-Hydroxypropanoic acid (Lactic acid), 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid), 2-Hydroxybutanoic acid, 2-Hydroxypentanoic acid, 2-Hydroxyhexanoic acid, 2-Hydroxyheptanoic acid, 2-Hydroxyoctanoic acid, 2-Hydroxynonanoic acid, 2-Hydroxydecanoic acid, 2-Hydroxyundecanoic acid, 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid), 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid), 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid), 2-Hydroxyoctadecanoic acid (Alpha hydroxysteraic acid), 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid).

18. The method of claim 9 wherein said aralkyl and aryl alpha hydroxyacid is selected from the group consisting of 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid), 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid, 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid), 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Chlorophenyl) 2-hydroxyethanioc acid, 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-Hydroxyphenyl) 2-hyroxypropanoic acid, or 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid.

19. The method of claim 9 wherein said polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid is at least one member selected from the group consisting of 2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid, threonic acid), 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid), 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid galactonic acid, talonic acid), 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.), 2-Hydroxypropane-1,3-dioic acid (Tartronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid), 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid, etc.), or lactone forms (gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, galactoheptonolactone, etc.).

20. The method of claim 9 wherein said alpha ketoacid and its ester is at least one member selected from the group consisting of 2-Ketoethanoic acid (Glyoxylic acid), Methyl 2-ketoethanoate, 2-Ketopropanoic acid (Pyruvic acid), Methyl 2-ketopropanoate (Methyl pyruvate), Ethyl 2-ketopropanoate (Ethyl pyruvate), Propyl 2-ketopropanoate (Propyl pyruvate), 2-Phenyl-2-ketoethanoic acid (Benzolyformic acid), Methyl 2-phenyl-2-ketoethanoate (Methyl benzolyformate), Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzolyformate), 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), Methyl 3-phenyl-2-ketopropanoate (Methyl phenylpyruvate), Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate), 2-Ketobutanoic acid, 2-Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketoheptanoic acid, 2-Ketooctanoic acid, 2-Ketododecanoic acid, and Methyl 2-ketooctanoate.

* * * * *

# EXHIBIT A
# (Part 2)

US005091171B1

# REEXAMINATION CERTIFICATE (2684th)

## United States Patent [19]

**Yu et al.**

[11] **B1 5,091,171**

[45] Certificate Issued **Sep. 26, 1995**

[54] **AMPHOTERIC COMPOSITIONS AND POLYMERIC FORMS OF ALPHA HYDROXYACIDS, AND THEIR THERAPEUTIC USE**

[76] Inventors: **Ruey J. Yu**, 4 Lindenwold Ave., Ambler, Pa. 19002; **Eugene J. Van Scott**, 3 Hidden La., Abington, Pa. 19001

**Reexamination Request**
No. 90/002,911, Dec. 17, 1992

**Reexamination Certificate for:**

| | |
|---|---|
| Patent No.: | **5,091,171** |
| Issued: | **Feb. 25, 1992** |
| Appl. No.: | **393,749** |
| Filed: | **Aug. 15, 1989** |

**Related U.S. Application Data**

[63] Continuation-in-part of Ser. No. 945,680, Dec. 23, 1986, abandoned, and a continuation of Ser. No. 469,738, Jan. 19, 1990.

[51] **Int. Cl.**[6] ..... **A61K 31/66**; A61K 31/70; A61K 31/19

[52] **U.S. Cl.** ..... **424/642**; 424/691; 514/2; 514/12; 514/19; 514/23; 514/114; 514/349; 514/399; 514/419; 514/518; 514/557; 514/561; 514/562; 514/567; 514/532; 514/547; 514/558; 514/570; 514/574; 514/577; 514/941; 514/844

[58] **Field of Search** ..... 424/642, 691; 514/2, 12, 19, 114, 349, 399, 419, 518, 532, 547, 23, 558, 561, 562, 567, 947, 873, 570, 494, 577, 847, 863

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(List continued on next page.)

*Primary Examiner*—Philip T. Datlow

[57] **ABSTRACT**

Preventive as well as therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxyacids, alpha ketoacids, related compounds or polymeric forms of hydroxyacids is disclosed. The cosmetic conditions and the dermatologic disorders in which the amphoteric compositions and the polymeric compounds may be useful include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, kyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging, and skin requiring cleansers.

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# REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

**Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.**

**ONLY THOSE PARAGRAPHS OF THE SPECIFICATION AFFECTED BY AMENDMENT ARE PRINTED HEREIN.**

**Column 3, lines 35–48:**

**Amphoteric substances by definition should behave either as an acid or a base, and can be an organic or an inorganic compound. The molecule of an organic amphoteric compound should consist of at least one basic and one acidic group. The basic groups include, for example, amino, imino and guanido groups. The acidic groups include, for example, carboxylic, phosphoric and sulfonic groups. Some examples of organic amphoteric compounds are [axino]** *amino* acids, peptides, polypeptides, proteins, creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuramic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine and deacetylated chondroitin.

**Column 5, lines 1–11:**

**The related amino acids include homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, 3-aminopropanoic acid, theanine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl- 3-aminopropanoic acid, 2,6-diaminopimelic acid, 2-amino- 3-phenylbutanoic acid, phenylglycine, canavanine, [canal ine]** *canaline*, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β-lysine, 2,4-diaminobutanoic acid, **[**2,3-diaminoproparoic acid**]** *2,3- diaminopropanoic acid*, 2-methylserine, 3-phenylserine and betaine.

**Column 6, line 50:**

**[**$(C_{16}H_{34})$**]** ($C_{16}H_{33}$) (H) C (OH) COOH

**Column 7, lines 1–3:**

6. 2-(4'-Chlorophenyl) 2-hydroxyethanoic acid (4-Chloromandelic acid) (Cl-$C_6H_4$) (H) (OH) COOH

Column 7, lines 26–38:

3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid) $HOCH_2$ (HO)**[**$CH_2$**]** *CH* (HO) **[**$CH_2$**]** *CH* (H) C (OH) COOH
4. **[**2,3,4,5,6-Pentahydroxyhexancic**]** *2,3,4,5,6-Pentahydroxyhexanoic* acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid) $HOCH_2$ (HO)**[**$CH_2$**]** *CH* (HO)**[**$CH_2$**]** *CH* (H) C (OH) COOH
5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.) $HOCH_2$



(HO)**[**$CH_2$**]** *CH* (HO)**[**$CH_2$**]** *CH* (HO)**[**$CH_2$**]** *CH* (HO**[**$CH_2$**]** *CH* (H) C (OH) COOH

Column 8, lines 39–40:

7. 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid) $C_6H_5$ CO COOH

Column 9, lines 43–66:

The acyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

H [—O—C(Ra)(Rb)—CO—]n OH

wherein Ra,Rb=H, alkyl, aralkyl ar aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=**[**1**]**2 or any numerical number, with a preferred number of up to 200. Ra and Rb in monomer unit 2, 3, 4 and so on may be the same or the different groups from that in monomer unit 1. For example, Ra,Rb=H in monomer unit 1, and Ra=$CH_3$,Rb=H in monomer unit 2 when n=2 is a dimer called lactyl glycollate, because the first monomer is glycollate unit and the second monomer is lactic acid unit. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms. The dimer and polymer of a hydroxycarboxylic acid may be present as a free acid, ester or salt form with organic base or inorganic alkali.

Column 10, lines 38–65:

(b) Cyclic ester. The cyclic ester of a hydroxycarboxylic acid may also be a dimer or polymer, the most common type however, is a dimer form. The cyclic dimer may be formed from an identical monomer or different monomers. For example, glycolide is formed from two molecules of glycolic acid by removing two molecules of water, and lactide is formed from two molecules of lactic acid in the same manner. The cyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

[—O—C(Ra)(Rb)—Co—]n

wherein Ra,Rb=H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=**[1]** *2* or any **[**numerical**]** number**[**, however with a preferred number of 2**]** *up to 200*. Ra and Rb in units 1, 2, 3 and so on may be the same or the different groups. For example, in glycolide Ra and Rb are H in both units 1 & 2, but in lactoglycolide Ra is H in unit 1, $CH_3$ in unit 2 and Rb is H in both unit 1 & 2. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 to carbon atoms.

Column 14, lines 17–34:

Since dimeric and polymeric forms of hydroxyacids are less stable in the presence of water or the like vehicle,

cosmetic and pharmaceutical compositions should be prepared as anhydrous formulations. Typical vehicles suitable for such formulations include mineral oil, petrolatum, isopropyl myristate, isopropyl palmitate, diisopropyl adipate, occtyl palmitate, acetone, squalene, squalane, silicone oils, vegetable oils and the like. Therapeutic compositions containing dimeric or polymeric forms of hydroxyacids do not require any incorporation of an amphoteric or pseudoamphoteric compound. The concentration of the dimeric or polymeric form of a hydroxyacid used in the composition may range from 0.1 to 100%, the preferred concentration ranges from *1* to 40%. Therapeutic compositions may be formulated as anhydrous solution, lotion, ointment, spray, powder or the like.

Column 15, lines 10–13:

An amphoteric composition containing *1* M 2-hydroxyethanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

Column 16, lines 46–56:

An amphoteric composition containing *1* M 2-hydroxypropanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.6. An amphoteric composition formulated from *1* M 2-hydroxypropanoic acid and 1 M L-lysine has pH 8.4.

Column 17, lines 7–14:

2-Hydroxypropanoic acid 9.0 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.3. The composition has pH 4.4 when *1* M instead of [b] 0.5 M creatinine is incorporated into the formulation.

Column 17, lines 17–20:

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and *1* M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

Column 18, lines 46–50:

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 25 ml of water. The solution thus obtained is mixed with an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated [for] *has* pH 4.6.

Column 20,lines 6–11:

DL-Tartaric acid 15.0 g and creatinine 11.3 g are dissolved in 35 ml of water. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH [s] 3.4.

Column 20,lines 62–64:

A pseudoamphoteric[:] composition containing 1 M pyruvic acid and 1 M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

Column 21, lines 32–36:

Benzilic acid 11.4 *g* and creatinine 5.7 g are dissolved in water 40 ml and pyropylene glycol 20 ml. Sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9.

Column 21,lines 54–57:

A pseudoamphoteric composition containing in combination 0.5 [m] *M* 2-hydroxyethanoic acid and 0.05% betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

Column 25,line 22:

*1.* Common dry skin.

Column 28,line 27:

5. Oily Skin and Skin [Cleanse] *Cleanser.*

Column 31,line 54–Column 32, line 3:

Fungal infections of the nails are very difficult to treat, because antifungal products to date are not therapeutically effective for topical treatment of nails. One of the reasons is that most antifungal drugs have not been formulated as bioavailable forms in the commercial products. When [tow nails] *toenails* were involved in the infections, patients were provided with amphoteric or pseudoamphoteric compositions containing in combination an antifungal agent and an alpha hydroxyacid or an alpha ketoacid at higher concentrations ranging from 20 to 99%, dispensed as 1–2 ml aliquots in small vials. The patients were instructed to apply topically the compositions discreetly to the infected nail surface by means of a fine calibre paint brush. the technique was the same as for application of nail polish, that is careful avoidance of contact with lateral nail folds or any periungual skin. Once or twice daily applications were continued for 2 to 8 weeks.

Column 33,lines 21–32:

2-Phenyl 2-hydroxyethanoic acid (Mandelic acid), 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid), 3 -Phenyl 2-hydroxypropanoic acid (Phenyllactic acid), 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Clorophenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxy-4'-methoxyphenyl 2 -hydroxyethanoic acid, 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-Hydroxyphenyl) [Hydroxyphenyl)] 2-hydroxypropanoic acid, 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid.

Column 34, lines 12–17:

The dimeric and polymeric forms of alpha hydroxyacids and the related [comopounds] *compounds* which may be incorporated into the compositions of the instant invention include [a cyclic] *acyclic* esters and cyclic ester; for example, glycolyl glycollate, lactyl lactate, glycolide, lactide, polyglycolic acid and polylactic acid.

Column 34, line 27:

[I] *We* claim:

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **8** and **12** are cancelled.

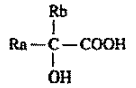
Claims **1–2, 5–7, 9–11, 14, 15,** and **17–19** are determined to be patentable as amended.

Claims **3–4, 13, 16** and **20,** dependent on an amended claim, are determined to be patentable.

New claims **21–27** are added and determined to be patentable.

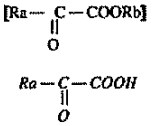
**1.** A composition [comprising in combination] *consisting essentially of* an amphoteric or pseudoamphoteric agent and an alpha hydroxyacid, an alpha ketoacid or a related compound present in a therapeutically effective amount in a [pharmaceutically] *topically* acceptable vehicle for topical treatment of cosmetic conditions or dermatologic disorders, said amphoteric or pseudoamphoteric agent being at least one member selected from the group consisting of [amino acids,] dipeptides, [polypeptides, proteins,] creatine, aminoaldonic acid, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, disulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, creatinine, [stearamidoethyl diethylamine, stearamidoethyl diethanolamine, stearaminopropyl dimethylamine, cocoamphoglycino cocoamphopropionate, cocoampho, propylsulfonate, phosphatidyl, ethanol-amine,] *cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidyl ethanolamine, glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, asparagine, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxypropoline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline,* phosphatidylserine and sphingomyelin, [and zinc oxide and aluminum oxide,] said amphoteric or pseudoamphoteric agent being present in a concentration effective to form an amphoteric or pseudoamphoteric system with said alpha hydroxyacid, alpha ketoacid or related compound;

said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid having the following chemical structure:



wherein Ra and Rb *independently* are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers[, and] *as* D, L, and DL forms when Ra and Rb are not identical;

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:



wherein Ra [and Rb are] *is* H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid [or an ester form,] or in a salt form with an organic base or an inorganic alkali; and

said related compound being at least-one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, aleuritic acid and pantoic acid.

**2.** The composition of claim **1** wherein said amphoteric or pseudoamphoteric agent is at least one member selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, [aspartic acid,] asparagine, [glutamic acid,] glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, proline, homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, aminoaldonic acids, aminouronic acids, aminoaldaric acids, lauryl aminopropylglycine, neuraminic acid, desulfated [heparing] *heparin*, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine, deacetylated chondroitin, creatinine, [3-amniopropanoic acid,] 2-aminobutanoic acid, 4 -aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, theanine, phenylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, [homoarginine, 4-hydroxyhomoarginine, β-lysine,] 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, [2-methylserine, 3-phenylserine, beataine,] taurine, [cysteinesulfinic acid,] methionine sulfoxide, methionine sulfone, 3,5-diiodotyrosine, thyroxine, monoiodotyrosine, pipecolic acid,- 4-aminopipecolic acid, 4-methylproline, glycylglycine, carnosine, anserine, ophidine, homocarnosine, β-alanylarginine, glutathione, ophthalmic acid, norophthalmic acid, [bradykinin, glucagon, protamines, histones,] cocoamphoglycine, cocoamphopropionate, cocoamphopropylsulfonate, phosphatidylethanolamine, phosphatidylserine, [sphingomyeline, stearamidoethyl diethylamine, stearamidoethyl diethanolamine, stearamidopropyl dimethylamine, quaternary ammonium hydroxide, quaternium hydroxide, aluminum oxide or zinc oxide] *and sphingomyelin.*

**5.** The composition of claim **1** wherein said polyhydroxy

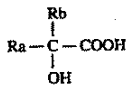
alpha hydroxyacid and polycarboxylic alpha hydroxyacid is at least one member selected from the group consisting of 2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid [() *and* Isomers[;] erythronic acid[,] *and* threonic acid[)], 2,3,4,5-Tetrahydroxypentanoic acid [() *and* Isomers[;] ribonic acid, arabinoic acid, xylonic acid[,] *and* lyxonic acid[)], 2,3,4,5,6-Pentahydroxyhexanoic acid [() *and* Isomers[;] allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid[,] *and* talonic acid[)], 2,3,4,5,6,7 Hexahydroxyheptanoic acid [)] *and* Isomers[;] glucoheptonic acid[,] *and* galactoheptonic acid [etc.)], 2-Hydroxypropane- 1,3-dioic acid ([Targtronic] *Tartronic* acid), 2 -Hydroxybutane-1,4-dioic acid (Malic acid), 2,3 -Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2 -carboxypentane-1,5-dioic acid (citric acid), 2,3,4,5 -Tetrahydroxyhexane-1,6-dioic acid [() *and* Isomers[;] saccharic acid[,] *and* mucic acid[, etc.)], or lactone forms [() Gluconolactone, [galactonolaotone] *galactonolactone*, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, [pantoyllact one] *pantoyllactone*, glucoheptonolactone, mannonolactone[,] *and* galactoheptonolactone[, etc.)].

**6**. The composition of claim **1** wherein said alpha ketoacid [and its ester] is at least one member selected from the group consisting of 2-Ketoethanoic acid (Glyoxylic acid), [Methyl 2-ketoethanoate,] 2-Ketopropanoic acid (Pyruvic acid), [Methyl 2-ketopropanoate (Methyl pyruvate), Ethyl 2-ketopropanoate (Ethyl pyuvate), Propyl 2 -ketopropanoate (Propyl pyruvate)], 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid), [Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate), Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate),] 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), [Methyl 3-phenyl-2-ketopropanoate (Methyl phenylpyruvate), Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate),] 2-Ketobutanoic acid, 2 -Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketoheptanoic acid, 2-Ketooctanoic acid[,] *and* 2-Ketododecanoic acid[, or Methyl2-ketooctanoate].

**7**. The composition of claim **1** wherein said cosmetic conditions, and dermatologic disorders include dry [sin] *skin*, zerosis, ichthyosis, dandruff, brownish spots, keratoses, melasma, lentigines, age spots, liver spots, pigmented spots, wrinkles, blemishes, skin lines, oily skin, acne, warts, eczema, pruritic skin, psoriasis, inflammatory dermatoses, disturbed [deratinization] *keratinization*, skin changes associated with aging, nail or skin requiring cleansers, conditioning or treatment, and hair or scalp requiring shampooing or conditioning.

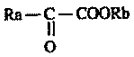
**9**. Method of topical treatment for [warts, nail infections, age spots,] wrinkles [and aging related skin changes] comprising topically applying [a therapeutically] *to a wrinkle an* effective amount *and for a period of time sufficient to visibly reduce said wrinkle*, of alpha hydroxyacids[,] *or* alpha ketoacids [or related compounds] in a [pharmaceutically] *topically* acceptable vehicle for topical treatment;

said alpha hydroxyacid being at least one member selected from the group consisting of alkyl alpha hydroxyacid, aralkyl and aryl alpha hydroxyacid, polyhydroxy alpha hydroxyacid and polycarboxylic alpha hydroxyacid represented by the following chemical structure:



wherein Ra and Rb *independently* are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha hydroxyacid existing as a free acid or lactone form, or in salt form with an organic base or an inorganic alkali, and as stereoisomers as D, L, and DL forms when Ra and Rb are not identical;

said alpha ketoacid being at least one member selected from a group of compounds represented by the following chemical structure:

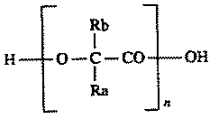


wherein Ra and Rb *independently* are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms, said alpha ketoacid existing as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali[; and

said related compound being at least-one member selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, and agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid].

**10**. The method of claim **9** wherein said alpha hydroxyacids[,] *or* alpha ketoacids [or related compound] is selected from the group consisting of *2-hydroxyethanoic* acid, 2-hydroxypropanoic acid, 2-methyl2-hydroxypropanoic acid, 2-phenyl2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate or ethyl 2-ketopropanoate.

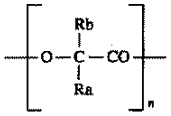
**11**. A therapeutic composition for topical treatment of cosmetic conditions or dermatologic disorders comprising [dimeric or polymeric forms of] *acyclic esters of* hydroxyacids [, represented by the following chemical formula:



wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and n=2 or any number up to 200; Ra and Rb in monomer unit 2 through 200 may be the same or the different groups from that in monomer unit 1; the hydrogen atom

in Ra and Rb may be substituted by a halogen atom-or a radical of lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 9 carbon atoms, or cyclic form having 5 to 6 ring members, and the dimeric and polymeric forms of hydroxyacids being present as a free acid, ester or in a salt form with an organic base or inorganic alkali in a pharmaceutically acceptable vehicle] *selected from the group consisting of glycolyl glycollate, mandelyl mandellate, atrolactyl atrolacate, phenyllactyl phenyllactate, benzilyl benzillate, glycolyl lactate and lactyl glycollate.*

**14**. A therapeutic composition for topical treatment of cosmetic conditions or dermatologic disorders, comprising [dimeric or polymeric forms] *cyclic esters* of hydroxyacids represented by the following chemical structure:




wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain, having 1 to 25 carbon atoms, or cyclic form having 5 or 6 ring members, and n=2 or any number up to 200, and Ra or Rb may be identical or not identical in the monomer units in a pharmaceutically acceptable vehicle.

**15**. The composition of claim **14** wherein said [dimeric or polymeric forms] *cyclic esters* of hydroxyacids are selected from the group consisting of glycolide, lactide, mandelide, atrolactide, phenyllactide, benzilide, methyllactide, lactoglycolide or glycolactide.

**17**. The method of claim **9** wherein said alkyl alpha hydroxyacid is at least one member selected from the group consisting of 2-Hydroxyethanoic acid (Glycolic acid), 2-Hydroxypropanoic acid (Lactic acid), 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid), 2-Hydroxybutanoic acid, 2-Hydroxypentanoic acid, 2-Hydroxyhexanoic acid, 2-Hydroxyheptanoic acid, 2-Hydroxyoctanoic acid, 2-Hydroxynonanoic acid 2-Hydroxydecanoic acid, 2-Hydroxyundecanoic acid, 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid), 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid), 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid), 2-Hydroxyoctadecanoic acid (Alpha [hydroxysteraic] *hydroxystearic* acid), 2-Hydroxyeicosanoic acid (alpha hydroxyarachidonic acid).

**18**. The method of claim **9** wherein said aralkyl and aryl alpha hydroxyacid is selected from the group consisting of 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid), 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid), 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid), 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Chlorophenyl) 2-[hydroxyethanioc] *hydroxyethanoic* acid, 2-(3'Hydroxy-4' -methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Hydroxy-3' -methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-Hydroxyphenyl) 2-[hyroxypropanoic] *hydroxypropanoic* acid, or 2-(3'+,4' -Dihydroxyphenyl) 2-hydroxyethanoic acid.

**19**. The method of claim **9** wherein said polyhydroxy alpha hydroxyacid or polycarboxylic alpha hydroxyacid is at least one member selected from the group consisting of 2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid [(] *and* Isomers[;] erythronic acid[,] *and* threonic acid[, threonic acid)], 2,3,4,5 -Tetrahydroxypentanoic acid [(] *and* Isomers[;] ribonic acid, arabinoic acid, xylonic acid[,] *and* lyxonic acid[)] 2,3,4,5,6-Pentahydroxyhexanoic acid [(] *and* Isomers[;] allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid[,] *and* talonic acid[)] 2,3,4,5,6,7 Hexahydroxyheptanoic acid [(] *and* Isomers[;] Glucoheptonic acid[,] *and* galactoheptonic acid[, etc.)], 2-Hydroxypropane-1,3-dioic acid (Tartronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2, 3 -Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2 -carboxypentane-1,5-dioic acid (Citric acid), 2,3,4,5-Tetrahydroxyhexane- 1,6-dioic acid [(] *and* Isomers[;] saccharic acid[,] *and* mucic acid[,etc.)], or lactone forms [(]gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone[,] *and* galactoheptonolactone[, etc)].

*21. Method of topical treatment for wrinkles comprising topically applying to a wrinkle an effective amount and for a period of time sufficient to visibly reduce said wrinkle, of a compound present in a topically acceptable vehicle, said compound selected from the group consisting of ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-hydroxynervonic acid, aleuritic acid and pantoic acid.*

*22. A method according to claim 9, wherein said alpha hydroxyacid or alpha ketoacid is present as the principal ingredient for effecting said reduction of a wrinkle.*

*23. A method according to claim 19, wherein said alpha hydroxyacid or alpha ketoacid is present as the principal ingredient for effecting said reduction of a wrinkle.*

*24. A method according to claim 9, wherein said wrinkle is caused by natural or innate aging.*

*25. A method according to claim 9, wherein said wrinkle is caused by actinic radiation or sun damage.*

*26. A method according to claim 9, wherein said wrinkle is a fine wrinkle.*

*27. A method according to claim 9, wherein said wrinkle is a coarse wrinkle.*

* * * * *

US005091171B1

# REEXAMINATION CERTIFICATE (3266th)

## United States Patent [19]

[11] B3 5,091,171

Yu et al.

[45] Certificate Issued Jul. 15, 1997

[54] **AMPHOTERIC COMPOSITIONS AND POLYMERIC FORMS OF ALPHA HYDROXYACIDS, AND THEIR THERAPEUTIC USE**

[75] Inventors: **Ruey J. Yu**, Ambler; **Eugene J. Van Scott**, Abington, both of Pa.

[73] Assignee: **Tristrata Technology, Inc.**, Wilmington, Del.

**Reexamination Request:**
No. 90/004,430, Oct. 28, 1996

**Reexamination Certificate for:**

| | |
|---|---|
| Patent No.: | **5,091,171** |
| Issued: | **Feb. 25, 1992** |
| Appl. No.: | **393,749** |
| Filed: | **Aug. 15, 1989** |

Reexamination Certificate B1 5,091,171 issued Sep. 26, 1996

**Related U.S. Application Data**

[63] Continuation-in-part of Ser. No. 945,680, Dec. 23, 1986, abandoned, and a continuation of Ser. No. 469,738, Jan. 19, 1990.

[51] **Int. Cl.**[6] ..... **A61K 31/66**; A61K 31/70; A61K 31/19

[52] **U.S. Cl.** ..... **424/642**; 424/691; 514/2; 514/12; 514/19; 514/23; 514/114; 514/349; 514/399; 514/419; 514/518; 514/557; 514/561; 514/562; 514/567; 514/532; 514/547; 514/558; 514/570; 514/574; 514/941; 514/844

[58] **Field of Search** ..... 424/642, 691; 514/2, 12, 19, 23, 114, 349, 399, 419, 518, 557, 561, 562, 567, 532, 547, 558, 570, 574, 941, 844

[56] **References Cited**

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*Primary Examiner*—James J. Seidleck

[57] **ABSTRACT**

Preventive as well as therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxyacids, alpha ketoacids, related compounds or polymeric forms of hydroxyacids is disclosed. The cosmetic conditions and the dermatologic disorders in which the amphoteric compositions and the polymeric compounds may be useful include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, kyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging, and skin requiring cleansers.

1

## REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

2

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **1–7, 9–11** and **13–27** is confirmed.

Claims **8** and **12** were previously cancelled.

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# EXHIBIT B

US005547988A

# United States Patent [19]

Yu et al.

[11] Patent Number: 5,547,988

[45] Date of Patent: *Aug. 20, 1996

[54] **ALLEVIATING SIGNS OF DERMATOLOGICAL AGING WITH GLYCOLIC ACID, LACTIC ACID OR CITRIC ACID**

[75] Inventors: **Ruey J. Yu**, Ambler; **Eugene J. Van Scott**, Abington, both of Pa.

[73] Assignee: **Tristrata Technology, Inc.**, Wilmington, Del.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,091,171.

[21] Appl. No.: **359,939**

[22] Filed: **Dec. 20, 1994**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 117,559, Sep. 7, 1993, abandoned, which is a continuation of Ser. No. 936,863, Aug. 27, 1992, abandoned, which is a continuation of Ser. No. 683,437, Apr. 10, 1991, abandoned, which is a continuation-in-part of Ser. No. 469,738, Jan. 19, 1990, abandoned, which is a continuation of Ser. No. 945,680, Dec. 23, 1986, abandoned, and a continuation-in-part of Ser. No. 393,749, Aug. 15, 1989, Pat. No. 5,091,171.

[51] **Int. Cl.**[6] ..... **A61K 7/48**; A61K 31/19

[52] **U.S. Cl.** ..... **514/557**; 514/574; 514/844; 514/847; 514/873

[58] **Field of Search** ..... 514/557, 844, 514/847, 873, 574

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*Primary Examiner*—Philip I. Datlow

*Attorney, Agent, or Firm*—Foley & Lardner

[57] **ABSTRACT**

Uses of topical compositions comprising a 2-hydroxycarboxylic acid or related compound to alleviate or improve signs of skin, nail and hair changes associated with intrinsic or extrinsic aging are disclosed. 2-Hydroxycarboxylic acids and their related compounds include, for example, 2-hydroxyethanoic acid, 2-hydroxypropanoic acid 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-hydroxybutane-1,4-dioicacid, 2,3-hihydroxybutane-1,4-dioic acid, 2-carboxy 2-hydroxypentane-1,5-dioic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate, ethyl 2-ketopropanoate, and gluconolactone. Topical application of compositions comprising 2-hydroxycarboxylic acid and/or related compounds has been found to alleviate or improve skin lines; blotches; blemishes; nodules; wrinkles; pigmented spots; atrophy; precancerous lesions; elastotic changes characterized by leathery, coarse, rough, dry and yellowish skin; and other skin changes associated with intrinsic aging or skin damages caused by extrinsic factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke and cigarette smoking. Topical applications of such compositions have also been found to improve the overall qualities of nail and hair affected by intrinsic aging or damaged by extrinsic factors.

**14 Claims, No Drawings**

# ALLEVIATING SIGNS OF DERMATOLOGICAL AGING WITH GLYCOLIC ACID, LACTIC ACID OR CITRIC ACID

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/117,559, filed Sep. 7, 1993, now abandoned, which is a continuation of Ser. No. 07/936,863, filed Aug. 27, 1992, now abandoned, which is a continuation of Ser. No. 07/683,437, filed Apr. 10, 1991, now abandoned, which is a continuation-in-part of Ser. No. 07/469,738, filed Jan.9, 1990, now abandoned, which is a continuation of Ser. No. 06/945,680, filed Dec. 23, 1986, now abandoned. This application is also a continuation-in-part of Ser. No. 07/393,749, filed Aug. 5, 1989, now U.S. Pat. No. 5,091,171.

## FIELD OF THE INVENTION

This application relates to topical compositions containing a 2-hydroxycarboxylic acid or a related compound for use in alleviating or improving the dermatological signs of aging, including changes or damage to skin, nail and hair associated with intrinsic aging, as well as changes or damage caused by extrinsic factors such as sunlight, radiations, air pollution, wind, cold, heat, dampness, chemicals, smoke, and cigarette smoking.

## BRIEF DESCRIPTION OF THE PRIOR ART

In our U.S. Pat. No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoses" we described and claimed the use of topical compositions containing an alpha hydroxyacid to alleviate the symptoms of ichthyosis. In our U.S. Pat. No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of topical compositions containing an alpha hydroxyacid to alleviate the symptoms of acne. In our U.S. Pat. No. 3,984,566 entitled "Method of Alleviating the Symptoms of Dandruff" we described and claimed the use of topical compositions containing an alpha hydroxyacid to improve the symptoms of dandruff.

In our U.S. Pat. No. 4,105,783 entitled "Therapeutic Treatment of Dry Skin"; U.S. Pat. No. 4,197,316 entitled "Treatment of Dry Skin"; and U.S. Pat. No. 4,380,549 entitled "Topical Treatment of Dry Skin"; we described and claimed the use of topical compositions containing an alpha hydroxyacid to alleviate or improve the symptoms of dry skin. In our U.S. Pat. No. No. 4,234,599 entitled "Treatment of Skin Keratoses with Alpha Hydroxyacids and Related Compounds", we described and claimed the use of topical compositions containing an alpha hydroxyacid or the related compound to alleviate the symptoms of actinic or nonactinic skin keratoses. In our U.S. Pat. No. 4,363,815 entitled "Alpha Hydroxyacids, Alpha Ketoacids and Their Use in Treating Skin Conditions", we described and claimed the use of topical compositions containing certain alpha hydroxyacids or the related compounds to improve skin conditions characterized by inflammation or disturbed keratinization.

In a report entitled "Topical Tretinoin for Photoaged Skin" by Albert M. Kligman, Gary L. Grove, Ryoji Hirose and James J. Leyden published in J. American Academy of Dermatology Vol. 15, pages 836–859, 886–887, 1986, daily topical application of 0.05% tretinoin (also known as all-trans retinoic acid) in a cream has been found to improve photodamaged skin. In another report entitled "Topical Tretinoin Improves Photoaged Skin: A Double-blind Vehicle-controlled Study" by Jonathan S. Weiss, Charles N. Ellis, John T. Headington, Theresa Tincoff, Ted A. Hamilton and John J. Voorhees published in J American Medical Association Vol. 259 pages 527–532, 1988, daily topical application of 0.1% tretinoin as compared to vehicle alone application for 16 weeks has been shown to improve photoaged skin. One side-effect has been a dermatitis encountered by 92% of the patients participating in this study. The dermatitis was characterized by a patchy erythema, localized swelling, dry skin, and mild scaling. Patients complained about burning, tingling, or pruritus. In yet another report entitled "Topical Tretinoin in the Treatment of Aging Skin" by Jonathan S. Weiss, Charles N. Ellis, John T. Headington and John J. Voorhees published in J. American Academy of Dermatology Vol. 19, pages 169–175, 1988, topical application of 0.1% tretinoin cream for 8 to 12 months has been found to improve clinical signs of aging skin. The side effects have been burning sensation in the eyes and mild skin irritations.



Parent application Ser. No. 07/469,738 filed Jan. 19, 1990, now abandoned, described in addition to the main subject certain compositions containing hydroxycarboxylic acids and the related ketocarboxylic acids for topical treatment of wrinkles and skin changes associated with aging. The related application of Ser. No. 07/393,749, now U.S. Pat. No. 5,091,171 described in addition to the main subject a topical treatment to alleviate or remedy warts, nail infections, age spots, wrinkles and aging related skin changes with a composition containing certain alpha hydroxyacids or the related compounds. We have now discovered that 2-hydroxycarboxylic acids and related compounds have much broader utilization than previously disclosed.

## SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide methods and compositions which can alleviate signs of skin, nail and hair changes associated with intrinsic and/or extrinsic aging.

We have now discovered that 2-hydroxycarboxylic acids and related compounds have unusual qualities as well as broader utilities which have not been disclosed in the prior art. Topical applications of compositions containing a 2-hydroxycarboxylic acid or a related compound have been found to improve cosmetic as well as clinical signs of changes in skin, nails and hair associated with intrinsic aging, or the damages caused by extrinsic factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke, and cigarette smoking. The signs of skin changes associated with intrinsic aging and the skin damages caused by extrinsic factors include thinning of skin; deepening of skin lines; wrinkles; blemishes; blotches; nodules; atrophy; pigmented spots; precancerous lesions; elastotic changes characterized by leathery, coarse, rough, dry and yellowish skin; and telangiectatic skin. The signs of nails and hair changes associated with intrinsic aging and the damages caused by extrinsic factors include thinning, fragility, splitting, lack of luster, uneven surface, and loss of flexibility and elasticity. 2-Hydroxycarboxylic acids and their related compounds which are useful for topical treatment of skin, nail and hair changes associated with intrinsic and/or extrinsic aging include, inter alia, 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyehtanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-hy-

droxybutane-1,4-dioicacid, 2,3-dihydroxybutane-1,4-dioic acid, 2-carboxy 2-hydroxypentane-1,5-dioic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate, ethyl 2-ketopropanoate, and gluconolactone.

Additional objects and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and the advantages of this invention may be realized and obtained by means of the compositions and methods particularly pointed out in the appended claims.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Cutaneous aging is associated with intrinsic factors with or without the additional factors of extrinsic origin. The intrinsic aging is due to internal physiologic functions and is an inherent aging process of living beings, which has not been reversible nor preventable. However, a modification, improvement or alleviation of the signs associated with cutaneous aging is now possible in accordance with this invention. Extrinsic aging, on the other hand, is due to external factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke, and cigarette smoking. A modification, improvement or alleviation of the signs associated with the extrinsic aging of skin, nails and hair is also now possible in accordance with this invention. Moreover, in some cases, it may be possible to eradicate such signs of intrinsic and extrinsic aging.

In the protected areas of skin such as abdomen and upper arm, the signs of skin aging which are caused by intrinsic factors include progressive thinning of skin, deepening of skin lines, wrinkles, dry and lusterless skin surface, loss of skin elasticity and recoilability. In the sun exposed areas of skin such as face and hands, the signs of intrinsic aging plus those of photoaging include deep wrinkles; marked loss of elasticity and recoilability; coarse, uneven and dry skin; blemished and leathery skin; loss of skin lubricating substances; and increased numbers of blotches, nodules and pigmented spots.

Histologically, the qualities and quantities of elastin and collagen tissues are changed. Normal elastin in tissues is replaced by abnormal elastin characterized as solar elastosis, and the normal collagen fibers are decreased.

The signs of nail and hair changes associated with intrinsic aging and the damages caused by extrinsic factors include thinning of hair and nail plate; lack of lubricants and luster, and uneven surface of hair and nails; fragility and splitting of hair and nails; and reduction of flexibility, resiliency, and elasticity of hair and nails.

The conventional management for signs of aging skin has been the use of cosmetics as well as medical procedures such as phenol, trichloroacetic acid, and other chemical peels, and plastic surgery etc. Such medical procedures are costly and risky with serious side effects, and the treatments alter only the cosmetic appearance of the skin, without any significant modifications of the underlying aging process.

As mentioned in the previous section, recent medical reports claimed the use of topical compositions containing tretinoin to improve clinical signs of skin aging associated with intrinsic factors as well as the skin damages caused by sunlight. However, use of tretinoin has been associated with certain adverse skin reactions such as dry skin, scaling, burning, tingling, itching, erythema, skin dermatitis, localized swelling, and induction of photosensitivity.



We have now discovered that use of topical compositions containing 2-hydroxycarboxylic acid or related compounds are therapeutically effective in modification or eradication of clinical signs of cutaneous aging with minimal if any side effects or discomfort.

For convenience, the 2-hydroxycarboxylic acids and related compounds which may be used in accordance with this invention may be classified into three groups, namely (1) 2-hydroxycarboxylic acids, (2) 2-ketocarboxylic acids and esters thereof, and (3) other related compounds. The related compounds may include hydroxycarboxylic acids with the hydroxyl group at any position other than position 2, for example position 3, position 4 or position 5, as well as cyclic hydroxycarboxylic acids (e.g., ascorbic acid and quinic acid), and also may include ketocarboxylic acids and esters thereof. Preferred related compounds include 3-hydroxycarboxylic acids, and 2-ketocarboxylic acids and esters thereof.

### Group 1

The first group comprises organic carboxylic acids in which one hydroxy group is attached to the 2 position carbon atom of the acid. The generic structure of such 2-hydroxycarboxylic acids may be represented as follows:

$(R_a)$ $(R_b)$ C (OH) COOH

Where $R_a$ and $R_b$ may be the same or different and are independently selected from H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 29 carbon atoms, and in addition $R_a$ and $R_b$ may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. 2-Hydroxycarboxylic acids may be present as a free acid or lactone form, or in a salt form with an organic base or an inorganic alkali. 2-Hydroxycarboxylic acids may exist as stereoisomers as D, L, and DL forms when R, and $R_b$ are not identical.

Typical alkyl, aralkyl and aryl groups for R, and $R_b$ include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, decyl, dodecyl, hexadecyl, benzyl, and phenyl, etc. 2-Hydroxycarboxylic acids of the first group may be further divided into subgroups comprising (1) alkyl hydroxycarboxylic acids, (2) aralkyl and aryl hydroxycarboxylic acids, (3) polyhydroxy-carboxylic acids, and (4) hydroxy-polycarboxylic acids. The following are representative 2-hydroxycarboxylic acids in each subgroup.

(1) Alkyl Hydroxycarboxylic Acids

1. 2-Hydroxyethanoic acid (Glycolic acid, hydroxyacetic acid) (H) (H) C (OH) COOH
2. 2-Hydroxypropanoic acid (Lactic acid) ($CH_3$) (H) C (OH) COOH
3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid) ($CH_3$) ($CH_3$) C (OH) COOH
4. 2-Hydroxybutanoic acid ($C_2H_5$) (H) C (OH) COOH
5. 2-Hydroxypentanoic acid ($C_3H_7$) (H) C (OH) COOH
6. 2-Hydroxyhexanoic acid ($C_4H_9$) (H) C (OH) COOH
7. 2-Hydroxyheptanoic acid ($C_5H_{11}$) (H) C (OH) COOH
8. 2-Hydroxyoctanoic acid ($C_6H_{13}$) (H) C (OH) COOH
9. 2-Hydroxynonanoic acid ($C_7H_{15}$) (H) C (OH) COOH
10. 2-Hydroxydecanoic acid ($C_8H_{17}$) (H) C (OH) COOH
11. 2-Hydroxyundecanoic acid ($C_9H_{19}$) (H) C (OH) COOH
12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid) ($C_{10}H_{21}$) (H) C (OH) COOH

13. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid) ($C_{12}H_{25}$) (H) C (OH) COOH
14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid) ($C_{14}H_{29}$) (H) C (OH) COOH
15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid) ($C_{16}H_{33}$) (H) C (OH) COOH
16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid) ($C_{18}H_{37}$) (H) C (OH) COOH
17. 2-Hydroxytetraeicosanoic acid (Cerebronic acid) ($C_{22}H_{45}$) (H) C (OH) COOH
18. 2-Hydroxytetraeicosenoic acid (Alpha hydroxynervonic acid) ($C_{22}H_{43}$) (H) C (OH) COOH

(2) Aralky1 And Aryl 2-Hydroxycarboxylic Acids

1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid) ($C_6H_5$) (H) C (OH) COOH
2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid) ($C_6H_5$) ($C_6H_5$) C (OH) COOH
3. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid) ($C_6H_5CH_2$) (H) C (OH) COOH
4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Attolactic acid) ($C_6H_5$) ($CH_3$) C (OH) COOH
5. 2-(4'-Hydroxyphenyl ) 2-hydroxyethanoic acid (4-Hydroxymandelic acid) (HO—$C_6H_4$) (H) C (OH) COOH
6. 2-(4'-Chlorophenyl ) 2-hydroxyethanoic acid (4-Chloromandelic acid) (Cl—$C_6H_4$) (H) C (OH) COOH
7. 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid (3-Hydroxy-4-methoxymandelic acid) (HO—, $CH_3O$—$C_6H_3$) (H) C (OH) COOH
8. 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid (4-Hydroxy-3-methoxymandelic acid) (HO—, $CH_3O$—$C_6H_3$) (H) C (OH) COOH
9. 3-(2'-Hydroxyphenyl) 2 -hydroxypropanoic acid [3-(2'Hydroxyphenyl) lactic acid](HO—$C_6H_4$—$CH_2$) (H) C (OH) COOH
10. 3-(4'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(4'-Hydroxyphenyl) lactic acid ](HO—$C_6H_4$—$CH_2$) (H) C (OH) COOH
11. 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid (3,4-Dihydroxymandelic acid) (HO—,HO—$C_6H_3$) (H) C (OH) COOH

(3) Polyhydroxy-carboxylic Acids

1. 2,3-Dihydroxypropanoic acid (Glyceric acid) ($HOCH_2$) (H) C (OH) COOH
2. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid) ($HOCH_2$ HOCH) (H) C (OH) COOH
3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid) ($HOCH_2$ HOCH HOCH) (H) C (OH) COOH
4. 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid) ($HOCH_2$ HOCH HOCH HOCH) (H) C (OH) COOH
5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid ( Isomers; glucoheptonic acid, galactoheptonic acid etc.) ($HOCH_2$ HOCH HOCH HOCH HOCH) (H) C (OH) COOH

(4) Hydroxy-polycarboxylic Acids

1. 2-Hydroxypropane-l,3-dioic acid (Tartronic acid) (HOOC) (H) C (OH) COOH
2. 2-Hydroxybutane-l,4-dioic acid (Malic acid) (HOOC $CH_2$) (H) C (OH) COOH
3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid) (HOOC HOCH) (H) C (OH) COOH

2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid) ($HOOC\ CH_2)_2$ C (OH) COOH

2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid ( Isomers; saccharic acid, mucic acid etc. ) HOOC $(CHOH)_4$ COOH

The 2-hydroxycarboxylic acids may be present in forms other than the acid, such as, for example, salts or lactones. Typical lactone forms which may be used in accordance with this invention include, for example, gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, and galactoheptonolactone.

Group 2

The second group, which comprises compounds related to the 2-hydroxycarboxylic acids, includes organic carboxylic acids in which one keto group is attached to position 2 carbon atom of the acid. The generic structure of such 2-ketoacids may be represented as follows:

$(R_c)$ CO COO $(R_d)$

wherein $R_c$ and $R_d$ can be the same or different and are each selected from H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 29 carbon atoms, and in addition $R_c$ may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha ketoacids may be present as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for $R_c$ and $R_a$ include methyl, ethyl, propyl, 2-propyl, butyl, pentyl, hexyl, octyl, dodecyl, hexadecyl, benzyl and phenyl.

In contrast to 2-hydroxycarboxylic acids of the first group compounds, the ester form of 2-ketocarboxylic acids has been found to be therapeutically effective for signs and symptoms of cutaneous aging including intrinsic and extrinsic aging. For example, while methyl 2-hydroxypropanoate and ethyl 2-hydroxypropanoate have minimal effects, methyl 2-ketopropanoate and ethyl 2-ketopropanoate are therapeutically very effective. The real mechanism for such difference is not known. We have speculated that the ester form of the 2-ketocarboxylic acid is chemically and/or biochemically very reactive, and a free 2-ketocarboxylic acid may be released in the skin after penetration through the stratum corneum of the skin. The representative 2-ketocarboxylic acids and their esters of the second group are listed below:

1. 2-Ketoethanoic acid (Glyoxylic acid) (H) CO COOH
2. Methyl 2-ketoethanoate (H) CO $COOCH_3$
3. 2-Ketopropanoic acid (Pyruvic acid) $CH_3$ CO COOH
4. Methyl 2-ketopropanoate (Methyl pyruvate) $CH_3$ CO $COOCH_3$
5. Ethyl 2-ketopropanoate (Ethyl pyruvate) $CH_3$ CO $COOC_2H_5$
6. Propyl 2-ketopropanoate (Propyl pyruvate) $CH_3$ CO $COOC_3H_7$
7. 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid) $C_6H_5$ CO COOH
8. Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate) $C_6H_5$ CO $COOCH_3$
9. Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate) $C_6H_5$ CO $COOC_2H_5$

10. 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid) $C_6H_5CH_2$ CO COOH
11. Methyl 3-phenyl-2-ketopropanoate (Methyl phenylpyruvate) $C_6H_5CH_2$ CO $COOCH_3$
12. Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate) $C_6H_5CH_2$ CO $COOC_2H_5$
13. 2-ketobutanoic acid $C_2H_5$ CO COOH
14. 2-Ketopentanoic acid $C_3H_7$ CO COOH
15. 2-Ketohexanoic acid $C_4H_9$ CO COOH
16. 2-Ketoheptanoic acid $C_5H_{11}$ CO COOH
17. 2-Ketooctanoic acid $C_6H_{13}$ CO COOH
18. 2-Ketododecanoic acid $C_{10}H_{21}$ CO COOH
19. Methyl 2-ketooctanoate $C_6H_{14}$ CO $COOCH_3$

Group 3

The third group, which also comprises related compounds, includes, inter alia, hydroxycarboxylic acids where the hydroxy is at a position other than position 2, and cyclic hydroxycarboxylic acids which are useful for topical application to improve signs of aging skin and the cutaneous appendages. The members of this group, which are more conveniently identified by name than by generic structures, include ascorbic acid, quinic acid, isocitric acid, tropic acid (2-phenyl 3-hydroxypropanoic acid), trethocanic acid, 3-chlorolactic acid, citramalic acid, agaricic acid, aleuritic acid, pantoic acid, lactobionic acid and hexulosonic acid.

## Amplifying Bioactivities of Cosmetio and Pharmaceutical Agents

The compositions of present invention may contain one or more 2-hydroxycarboxylic acids or related compounds to magnify the therapeutic effect of an unrelated cosmetic or pharmaceutical agent. At least one compound selected from the group consisted of 2-hydroxycarboxylic acids and related compounds may be incorporated into a composition containing a cosmetic or pharmaceutical agent for topical treatment to improve or alleviate signs of skin, nails or hair changes associated with intrinsic aging or the damages caused by extrinsic factors. It has been found that such incorporation have resulted in magnified therapeutic efficacies which are not simply additive effects.

Most pharmaceutical drugs produce their therapeutic effects by first interacting with their receptors in the target tissues. Many drug receptors are functional macromolecules such as enzymes, cell membrane components or certain components of cells. The binding affinity or interacting property of a drug toward its specific receptor molecule is intimately governed by the chemical structure of the drug. Since most pharmaceutical agents are chemically different from 2-hydroxycarboxylic acids and related compounds, the respective receptor molecules should be different and so are the pharmacologic actions and the therapeutic effects. Under such conditions if 2-hydroxycarboxylic acid or a related compound is incorporated into a composition containing a pharmaceutical agent, one of the following two consequences may arise:

(a) No enhancement or any substantial changes in either effect. In this case, the overall clinical effect would be a mixing effect, i.e. the effect due to the pharmaceutical agent alone mixed with the effect due to the 2-hydroxycarboxylic acid or the related compound alone. Also in this case, the interaction between the pharmaceutical agent and its receptor molecule is not affected nor interfered by the presence of 2-hydroxycarboxylic acid or the related compound. Nor does 2-hydroxycarboxylic acid or the related compound assist in or enhance the binding affinity or the interaction of the pharmaceutical agent toward its receptor molecule. The clinical results from such combination composition would be just the mixing effects, and are predictable.

(b) Amplified therapeutic action or substantial loss of therapeutic action in either effect. In this case, the interaction between the pharmaceutical agent and its receptor molecule is affected either positively or negatively by the presence of 2-hydroxycarboxylic acid or the related compound. From the point of positive effect, 2-hydroxycarboxylic acid or the related compound may produce an amplified effect by either increasing the affinity of the receptor molecule toward the pharmaceutical agent; acting as a better and more efficient coenzyme or as an activator by disrupting barriers and removing obstacles for better binding of the agent toward its receptor molecule; for example, enzyme activation by removal of natural inhibitors. In all these cases the overall clinical results would be due to magnified therapeutic effects which are not predictable from either effect alone.

From the point of negative effect, a 2-hydroxycarboxylic acid or a related compound might interfere with or decrease the binding affinity of the pharmaceutical agent toward its receptor molecule; i.e. acting as an inhibitor. In such case, the overall clinical results should be due to a substantial diminishment or completely loss of therapeutic effects, which is also unpredictable from either effect alone.

We have found that, in most cases, therapeutic effects of cosmetic and pharmaceutical agents are amplified when a 2-hydroxycarboxylic acid or a related compound is incorporated into the composition, i.e., consequence (b) above is observed.

The cosmetic and pharmaceutical agents which may be actuated by 2-hydroxycarboxylic acids or related compounds include those that improve or eradicate age spots, keratoses and wrinkles by different mechanism of action; antimicrobial and antiacne agents; antipruritic and antixerotic agents; antiinflammatory agents; sunscreen and antiphotosensitive agents; nail and hair conditioners, cleansers, care and treatment agents; wart removers; skin lightening agents; depigmenting agents; local anesthetics and analgesics; corticosteroids; retinoids; vitamins; hormones; and antimetabolites.

Some examples of cosmetic and pharmaceutical agents include acyclovir, amphotericins, chlorhexidine, clotrimazole, ketoconazole, miconazole, metronidazole, minocycline, nystatin, neomycin, kanamycin, phenytoin, octyl dimethyl PABA, octyl methoxycinnamate, PABA and other esters, octyl salicylate, oxybenzone, dioxybenzone, tocopherol, tocopheryl acetate, selenium sulfide, zinc pyrithione, soluble elastin, diphenhydramine, pramoxine, lidocaine, procaine, erythromycin, tetracycline, clindamycin, hydroquinone and its monomethyl and benzyl ethers, naproxen, ibuprofen, cromolyn, retinoic acid, retinol, retinyl palmitate, retinyl acetate, coal tar, griseofulvin, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, minoxidil, dipyridamole, diphenylhydantoin, benzoyl peroxide and 5-fluorouracil.

## Specific Compositions For Skin And Skin Appendages

While 2-hydroxycarboxylic acids and related compounds are therapeutically effective for topical treatment to improve

or alleviate signs of skin, nail or hair changes associated with intrinsic aging and/or photoaging, certain compounds of the instant invention are more potent than others. In selecting a particular compound of the present invention two factors, namely (a) potency and (b) concentration have to be considered. If rapid results are preferred in certain cases, most potent compounds with highest and safe concentrations may be used. Under such conditions the treatment time is substantially shortened with good to excellent clinical results. Generally, such treatment has to be carried out under supervision by a dermatologist or trained professional in the office, medical center, skin care center, or beauty salon etc. Such procedure or treatment may include micro and semimicro peels, epidermolysis or superficial peel, and dermolysis or deeper peel.

Examples of more potent 2-hydroxycarboxylic acids and related compounds to be formulated in specific compositions include 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate. The concentration of 2-hydroxycarboxylic acid or the related compound used in such specific composition may range from an intermediate to a full strength, therefore the dispensing and the application require special handling and procedures.

If the 2-hydroxycarboxylic acid or the related compound at full strength (usually 85–100%) is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the liquid compound with or without a gelling agent is directly dispensed as 0.5 to 1 ml aliquots in small vials.

If the 2-hydroxycarboxylic acid or the related compound at full strength is a crystalline or solid form at room temperature such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid, the crystalline or solid compound is first dissolved in a minimal amount of vehicle or vehicle system prepared from water, ethanol, propylene glycol and/or butylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 ml, and the 70% strength solution thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used 0.1 to 2% of hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose, chitosan, carbomer, or polyquaternium-10 may be incorporated into the above solution.

To formulate an intermediate strength (usually 20–50%), 2-hydroxycarboxylic acid or the related compound either a liquid or solid form at room temperature is first dissolved in a vehicle or vehicle system prepared from water, acetone, ethanol, propylene glycol and/or butylene glycol. For example, 2-hydroxyethanoic acid or 2-ketopropanoic acid 30 g is dissolved in ethanol 56 g and propylene glycol 14 g, and the 30% strength solution thus obtained is dispensed as 7 to 14 ml aliquots in dropper bottles.

### General Preparation of Compositions

Most compositions of the instant invention may be formulated as solution, gel, lotion, cream, ointment, or other pharmaceutically acceptable form. To prepare a composition in solution form for general use, at least one 2-hydroxycarboxylic acid or related compound is dissolved in a solution prepared from ethanol, water, propylene glycol, butylene glycol, acetone or other pharmaceutically acceptable vehicle. The concentration of the 2-hydroxycarboxylic acid or related compound may range from 0.1 to 100 percent, the preferred concentration ranges being from about 2 to about 25 percent for home use, with higher ranges, e.g., from about 70 to about 100 percent being acceptable for office use where professional supervision is provided. Thus, such concentrations can also range from about 25 to about 50 percent and from about 50 to about 70 percent, with the proviso that concentrations of about 25 percent or more generally requiring profession supervision.

In the preparation of a composition in lotion, cream or ointment form, at least one of 2-hydroxycarboxylic acids or related compounds is initially dissolved in a solvent such as water, ethanol, butylene glycol, and/or propylene glycol. The solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment base such as hydrophilic ointment or petrolatum. The concentrations of 2-hydroxycarboxylic acids or related compounds used in the compositions are the same as described above.

Thin gel compositions are specifically useful for topical application to hair and face. A typical gel composition of the instant invention is formulated by dissolving at least one of 2-hydroxycarboxylic acids or related compounds in a vehicle prepared from ethanol, water, butylene glycol, and/or propylene glycol. A gelling agent such as xanthan gum, polyquaternium-10, methyl cellulose, ethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, chitosan, hydroxypropylmethylcellulose, ammoniated glycyrrhizinate or carbomer is then added to the solution with agitation. The preferred concentration of the gelling agent may range from 0.1 to 2 percent by weight of the total composition.

To prepare an actuated composition, a cosmetic or pharmaceutical agent is incorporated into any one of the above formulations by dissolving or mixing the agent into the composition.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limited. Therefore, any of the aforementioned 2-hydroxycarboxylic acids and related compounds may be substituted according to the teachings of this invention in the following examples.

### EXAMPLE 1

A typical solution composition containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows. 2-Hydroxyethanoic acid (glycolic acid) crystals 7 g is dissolved in water 50 ml and propylene glycol 15 ml. Ethanol is added to the solution until the total volume is 100 ml. The composition thus prepared contains 7% w/v 2-hydroxyethanoic acid.

### EXAMPLE 2

A typical gel composition containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

2-Hydroxypropanoic acid (DL-lactic acid) USP grade 5 g is dissolved in water 60 ml and butylene glycol 10 ml, and chitosan or polyquaternium-10 0.3 g is added with stirring. Ethanol is added to the mixture until the volume is 100 ml. The mixture is stirred until a uniform gel is obtained. The thin gel thus obtained contains 5% 2-hydroxypropanoic acid.

EXAMPLE 3

A typical oil-in-water emulsion containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

2-Methyl 2-hydroxypropanoic acid (methyllactic acid) crystals 10 g is dissolved in water 20 ml and concentrated ammonium hydroxide 2 ml is added to the solution. The solution is mixed with enough hydrophilic ointment USP to make a total weight of 100 g. The cream thus formulated contains 10% 2-methyl 2-hydroxypropanoic acid.

EXAMPLE 4

A typical water-in-oil emulsion containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

Gluconolactone 7 g is dissolved in water 12 ml and concentrated ammonium hydroxide 0.5 ml is added to the solution. The solution is mixed with enough water-in-oil emulsion to make a total weight of 100 g. The water non-washable cream thus formulated contains 7% gluconolactone.

EXAMPLE 5

A typical ointment containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid (mandelic acid) crystals 10 g is dissolved in 10 ml ethanol, and the solution thus formed is mixed with mineral oil 35 g and enough white petrolatum to make a total weight of 100 g. The ointment thus formulated contains 10% 2-phenyl 2-hydroxyethanoic acid.

EXAMPLE 6

A specific preparation containing a full strength or a high concentration of 2-hydroxycarboxylic acid or the related compound may be formulated and dispensed as follows.

If 2-hydroxycarboxylic acid or the related compound at full strength is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the compound is directly dispensed as 0.5 to 1 ml aliquots in small vials. If the compound is a crystalline or solid form, such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid and 2,2-diphenyl 2-hydroxyethanoic acid, the compound is first dissolved in minimal amount of an appropriate vehicle system selected from water, ethanol, propylene glycol and butylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 ml, and 70% strength 2-hydroxyethanoic acid with or without addition of 0.5% chitosan or polyquaternium-10 is dispensed as 1 to 5 ml aliquots in small vials.

EXAMPLE 7

A typical preparation containing an intermediate strength of 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

Malic acid, tartaric acid or citric acid 35 g is dissolved in water 60 ml and propylene glycol 5 ml. The 35% strength solution thus prepared is dispensed as 5 to 10 ml aliquots in dropper bottles.

EXAMPLE 8

A composition containing 2-hydroxycarboxylic acid or the related compound to magnify the therapeutic effect of a cosmetic or pharmaceutical agent for wrinkles and other signs of skin aging may be formulated as follows.

Ethyl 2-ketopropanoate (ethyl pyruvate) 2 g and all-trans retinoic acid 0.02 g are dissolved in a vehicle system prepared from ethanol 50 ml, water 28 ml and propylene glycol 20 ml. The composition thus formulated contains retinoic acid 0.02% and ethyl 2-ketopropanoate 2%.

EXAMPLE 9

A composition containing 2-hydroxycarboxylic acid or the related compound to amplify the therapeutic effect of a dermatologic agent for blemishes, pigmented spots and wrinkles may be formulated as follows.

2-Hydroxyethanoic acid 8 g, hydroquinone 2 g and sodium metabisulfite 0.4 g are dissolved in a vehicle prepared from ethanol 30 ml, water 45 ml and propylene glycol 15 ml. Chitosan or polyquaternium-10 0.3 g is added to the solution with stirring. The mixture is stirred until a uniform gel is obtained. The thin gel thus obtained contains hydroquinone 2% and 2-hydroxyethanoic acid 8%.

EXAMPLE 10

A typical cleansing and soothing composition containing 2-hydroxycarboxylic acid or the related compound to enhance the therapeutic effect of a dermatologic agent for initial treatment of hair or skin changes associated with aging may be formulated as follows.

2,2-Diphenyl 2-hydroxyethanoic acid (benzilic acid) 2 g and chlorhexidine 0.3 g are dissolved in a vehicle system prepared from ethanol 30 ml, water 58 ml and butylene glycol 10 ml. The solution thus formulated contains chlorhexidine 0.3% and 2,2-diphenyl 2-hydroxyethanoic acid 2%.

EXAMPLE 11

A typical lotion containing 2-hydroxycarboxylic acid or the related compound to substantiate and magnify the sunscreen effect of a dermatologic agent may be formulated as follows.

2-Hydroxyethanoic acid 3 g and concentrated ammonium hydroxide 0.75 ml are dissolved in water 7 ml, and the solution thus obtained is mixed with 85 g of an oil-in-water emulsion which contains octyl methoxycinnamate 5 g. The actuated sunscreen lotion thus formulated contains 5% sunscreen agent and 3% 2-hydroxyethanoic acid.

TEST RESULTS

(1) Biologic and Pharmacologic Actions

The skin may be classified into two major parts; dermis and epidermis. The dermis contains blood vessels, nerves, collagen, elastin etc, and fibroblast cells in the dermis are responsible for the biosynthesis of collagen and elastin. The epidermis contains nerves but no collagen, elastin, nor blood vessels.

The epidermis is further divided into two distinct zones; malpighian layer and horny layer. The malpighian layer, a living tissue, is further divided into basal, spinous, and granular layers. The horny layer, a dead tissue, is also called stratum corneum. In the natural process, basal cells in the

basal layer move outward through the spinous and granular layers to become dead cells called corneocytes, in the stratum corneum. The stratum corneum consists of approximately 14 layers of corneocytes. In normal skin it takes about 14 days for the basal cells to move from the basal layer to the end of the granular layer and to become corneocytes, and another 14 days to reach the outermost layer of the stratum corneum. This process of forming corneocytes is called keratinization, and stratum corneum, nail, and hair are the natural products produced by such process. The stratum corneum is the skin tissue that one feels when touching the skin. Usually, it takes about 28 days for cells of the basal layer to move outward to the surface in the course of making new skin.

We have found that compositions containing low concentrations of 2-hydroxycarboxylic acid or the related compound, when applied topically to the skin, diminish corneocyte cohesion in the stratum corneum. This effect predominantly occurs among corneocyte cells at inner levels of the stratum corneum, i.e. near the junction to the granular layer, and there is no effect among corneocyte cells at outer layers in the stratum corneum. Therefore, 2-hydroxycarboxylic acids and related compounds are not typical keratolytics such as strong acids, strong alkalis, thiols, urea and lithium salts which cause disaggregation of corneocyte cells in the outer layers of the stratum corneum.

We have also discovered that compositions containing intermediate to high concentrations of 2-hydroxycarboxylic acid or the related compound, when topically applied to the skin, cause profound beneficial effects in the dermis as well as the epidermis of the skin. The skin becomes thicker and plump as measured clinically by caliper and micrometer techniques. Histometric techniques using microscopic analysis of tissue biopsy specimens confirm that new and more collagen and elastic fibers have been biosynthesized in the dermis.

The biologic and pharmacologic actions of 2-hydroxycarboxylic acid or the related compound suggest that topical application of the composition should improve or alleviate signs of skin, nail, and hair changes associated with intrinsic and/or extrinsic aging.

(2) Therapeutic Effects

In order to determine whether compositions containing 2-hydroxycarboxylic acid or the related compound were therapeutically effective for topical application to improve or alleviate signs of skin, nail, and hair changes associated with intrinsic and/or extrinsic aging, a total of more than 120 volunteers and patients participated in these studies. Intrinsic aging is due to internal physiologic process, different from the damage caused by an external factor such as sunlight. The body areas showing predominantly intrinsic aging are in the protected regions of the skin such as abdomen, buttock, and upper arm. The signs of intrinsic aging include thinning of skin, deepening of natural skin lines, fine wrinkles, dry and lusterless skin surface, loss of skin elasticity and recoilability. Therefore, for intrinsic aging test compositions were topically applied to the skin of upper arms and/or abdomen.

The extrinsic aging is a progressive damage caused by environmental factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke, and/or smoking. The body areas predominantly involved are in the exposed regions of the skin such as face, scalp with thin or no hair, neck, forearms, and the back of hands. The signs of extrinsic aging in these skin areas are in most cases a combination of intrinsic aging and extrinsic aging unless it involves a very young person. The signs of both intrinsic and extrinsic aging include fine and deep wrinkles, loss of elasticity and recoilability, coarse and very dry skin, blemished and leathery skin, loss of skin lubricants, and increased numbers of age spots, blotches, nodules and pigmented spots. In such cases test compositions were topically applied to face, forearms, and the back of hands.

The composition containing a weak to intermediate concentration of 2-hydroxycarboxylic acid or the related compound was topically applied to the skin by a patient or a participating subject at home, as a home treatment. The composition containing a high concentration or a full strength of 2-hydroxycarboxylic acid or the related compound was topically applied to the involved skin of a patient, such as the face, by a dermatologist or a trained health professional as an office procedure or treatment. For rapid therapeutic results, both home and office treatments were adopted in many cases.

(a) Home Treatment

In order to determine whether the composition containing a 2-hydroxycarboxylic acid or related compound was therapeutically effective for topical application to alleviate or improve signs of skin changes associated with intrinsic and extrinsic aging on the face or the back of hands, both patients and volunteer subjects were included in the study. The compositions containing 5 to 30%, and preferably between 8 to 20%, of a 2-hydroxycarboxylic acid or related compound were formulated with optimal bioavailability of the active ingredient according to the examples. The participants were instructed to apply the compositions twice daily on the face and the back of hands for intervals of 2 to 12 months. All participants were instructed to avoid sun exposure, and to use a sunscreen product with a sun protection factor of 15 or greater if exposure to sunlight was unavoidable.

Photographs of each side of the face, and the back of hands were taken at the beginning of the study and repeated at one to three-month intervals. The participants were asked not to wear facial makeup nor to apply any products on the back of hands at the time of the visit, except for eye shadow if desired. Standardized photographic conditions were used: the same light source at two feet from the face aimed at a locus on the frontal aspect of each cheek, and also at two feet from the back of hands. Photographs were taken with the camera aimed perpendicular to the cheek or the back of hands.

After 2 months of home treatment all of a group of 35 participants showed substantial improvement of the face and the back of hands. The skin was smoother, glossy, and softer. Blotches, blemishes, and age spots on the face were also decreased in number or were lighter in color in a group of 30 out of 35 closely monitored participants. After 6 to 9 months of continued home treatment, skin lines and fine wrinkles on the face either disappeared or were diminished in 24 out of this group of 35 participants. Great numbers of age spots and blemishes on the face and the back of hands also continued to disappear or become much less conspicuous. The skin appeared and felt smooth, soft, and glossy. Coarser wrinkles were substantially reduced after 18 months of continued home treatment.

(b) Office Treatment

Specific compositions containing a high concentration to a full strength of a 2-hydroxycarboxylic acid or related compound were used in most cases as an office procedure or

treatment. The composition containing 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-ketopropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, or 2,2-diphenyl 2-hydroxyethanoic acid at concentrations of 50% or higher was prepared according to the examples.

The composition was topically applied to the skin and gently massaged in with the fingers or a cotton ball by a dermatologist or a trained health professional who wore rubber gloves. After 1 to a few minutes, depending on the strength used and the skin sensitivity of the subject, the skin was gently rinsed with water.

Such office treatment was repeated every 2 to 3 weeks. Photographs of the skin so treated were taken at the beginning of the study and repeated at one to three-month intervals as described in the previous section.

After one to two office treatments, all 32 patients in this particular study showed distinct improvement of the face and other areas treated, such as the forearms, the back and the back of hands. The original coarse, rough, and dry skin had improved markedly, and the skin was smooth, glossy, and soft. The number of blotches, blemishes, brownish spots, and age spots decreased significantly after 3 to 5 office treatments. Facial skin lines and fine wrinkles improved or disappeared in 25 out of this group of 32 patients after 8 to 12 office treatments.

(c) Office Treatment Plus Home Treatment

If rapid therapeutic results are desired, home treatment may be combined with the office treatment. After each office treatment, the patient would topically apply twice daily a composition containing a low to intermediate concentration of a 2-hydroxycarboxylic acid or related compound on the face and the back of hands.

After one office treatment plus twice daily home treatment, all 28 patients of this study showed marked improvement on the texture of treated skin. The rough, coarse, and dry skin disappeared, and the skin was smooth, glossy, and soft after one month. Blotches, blemishes, nodules, age spots, pigmented spots, skin lines, and fine wrinkles improved or disappeared, 3 to 5 months after the office treatment plus the home treatment. Deep wrinkles started to improve visibly as measured by photographic means after 5 to 10 months of sustained office treatments and continued home treatments.

Most patients showed marked improvement of deep wrinkles after 12 to 18 months of combined office and home treatments.

(d) Epidermolysis and Dermolysis

While the office procedure described in the previous section causes a micro or semimicro peeling of the skin, procedures which cause epidermolysis and dermolysis result in superficial and deeper peeling of the skin. When a composition containing a high concentration or a full strength of a 2-hydroxycarboxylic acid or related compound such as 70% 2-hydroxyethanoic acid, 85% 2-hydroxypropanoic acid, and 100% 2-ketopropanoic acid is topically applied to a photodamaged skin, epidermolysis will occur if the time of contact with the skin is long enough. The epidermolysis is clinically beneficial for topical treatment of acne, age spots, keratoses, pigmented spots, skin lines, blemishes, wrinkles and other signs of skin changes associated with intrinsic and extrinsic aging.

In general, epidermolysis of skin occurs faster on the face than on the upper back or the back of hands, and faster on skin of younger people than of older people and usually faster in women than men. The clinical sign of epidermolysis is blanching of the skin, a sign that signals the threshold between superficial peeling and deeper peeling. When blanching of the skin is first seen the skin is immediately rinsed with water to prevent a deeper peeling of the skin.

In dermatologic practice dermolysis or deep peeling has been induced for the treatment of blemished skin or aging skin by using peeling agents such as trichloroacetic acid and phenol. These peeling agents are very caustic to the skin and are also toxic. Serious side effects including death have been reported. A 2-hydroxycarboxylic acid or related compound can be safely used as a micro, semimicro, superficial or deep peeling agent for topical treatment of dermatologic disorders including skin changes associated with intrinsic aging or skin damages caused by extrinsic aging such as photoaging.

The face of a patient to be so treated was initially wiped with 70% ethanol, and the eyes were covered with wet cotton balls. A full strength (100%) 2-ketopropanoic acid, or an aqueous solution containing 70% 2-hydroxyethanoic acid or 85% 2-hydroxypropanoic acid was uniformly applied to the skin using a cotton ball. The patient usually feel a transient burning sensation. Erythema usually appeared after less than a minute up to a few minutes depending on the skin type, age, sex etc. The skin was rinsed with water after blanching of the skin occurred or intense erythema persisted.

A total of 23 patients participated in the epidermolysis study. Most participants also daily used emollient lotions or creams containing weak concentrations of a 2-hydroxycarboxylic acid or related compound. All the participants showed marked improvement of skin lines, blemishes and fine wrinkles after 2 months.

(3) Amplified Bioactivities

We have discovered that when a 2-hydroxycarboxylic acid or related compound is incorporated into a composition containing a dermatologic agent, the pharmacologic actions and the therapeutic effects are unexpectedly amplified in most cases. For example, a 2-hydroxycarboxylic acid or related compound magnifies the therapeutic effects of hydroquinone, 5-fluorouracil, chlorhexidine, clotrimazole, miconazole, tetracycline, retinoic acid etc. Compositions containing 2-hydroxycarboxylic acid or the related compound and a dermatological or other pharmaceutical agent were formulated according to the examples.

Each participating patient received two compositions; i.e. with or without the incorporation of a 2-hydroxycarboxylic acid or related compound. The patients were instructed to apply topically one medication on one side of the body such as on the back of the left hand and the other medication on the other side of the body such as on the back of the right hand. Specific instructions were given to the patients to apply the medications twice daily to the involved areas or lesions of blemishes, age spots, melasmas, lentigines, skin lines, wrinkles, or precancerous actinic keratoses. Clinical improvements were discernible after a few weeks to a few months of topical application. The sides treated with amplified compositions were substantially better than the sides treated with the medications which did not contain any 2-hydroxycarboxylic acid or the related compound.

(4) Hair and Nail Treatments

Compositions containing a 2-hydroxycarboxylic acid or related compound at low concentrations, preferably from i to 4%, for hair care and treatment were formulated according to the examples. A solution or thin gel form thus formulated

was topically applied to the hair after shampoo. The same treatment was repeated 3 to 4 times weekly. After a few weeks to a few months of such treatment, the signs of hair changes associated with intrinsic aging and the damages caused by photoaging started to improve substantially. The hair first appeared smooth and shiny. The hair became softer to the touch and feel. After a few months of such treatment, hair increased its elasticity and flexibility.

Compositions containing 2-hydroxycarboxylic acid or the related compound at intermediate concentrations, preferably from 8 to 20%, for nail care and treatment were formulated according to the examples. A solution or thin gel form thus prepared was topically applied twice daily to edges, surface and base of affected nail plates. After a few months of such treatment, the signs of nail changes associated with intrinsic and extrinsic aging started to improve noticeably. The nail looked glossy and felt smooth on the surface. The flexibility and elasticity of the nail after the treatment also increased. Brittleness diminished and the occurrence of terminal nail splitting became rare.

It will be apparent to those skilled in the art that various modifications and variations can be made to the compositions of matter and methods of this invention. Thus, it is intended that the present invention covers such modifications and variations.

What is claimed is:

**1**. A method for reducing the appearance of skin changes associated with intrinsic and/or extrinsic aging, said skin changes associated with aging resulting from natural or innate aging or exposure to actinic radiation,

whereby said skin changes associated with aging are selected from the group consisting of wrinkles, thinning of the skin, deepening of skin lines, yellowish skin, loss of elasticity, loss of recoilability, and loss of collagen,

said method comprising topically applying to an area of skin exhibiting said change a composition comprising a compound selected from the group consisting of glycolic acid, lactic acid, citric acid, or a topically effective salt thereof, in an amount and for a period of time sufficient to reduce the appearance of said skin changes associated with aging.

**2**. The method of claim **1**, wherein said extrinsic aging is caused by extrinsic factors selected from the group consisting of sunlight; radiation; air pollution; wind; cold; dampness; heat; chemicals; smoke; and cigarette smoking.

**3**. The method of claim **1**, wherein said compound is in the form of a salt.

**4**. A method according to claim **1**, wherein said composition is formulated as a solution, gel, lotion, cream, or ointment.

**5**. The method according to claim **1**, wherein the period of time is at least three months.

**6**. The method according to claim **1**, wherein the period of time is at least four months.

**7**. The method according to claim **1**, wherein said topical application is on a daily basis.

**8**. The method according to claim **1**, wherein said skin changes associated with aging result from natural or innate aging.

**9**. The method according to claim **1**, wherein said skin changes associated with aging result from exposure to actinic radiation.

**10**. The method according to claim **1**, wherein said compound is the principal ingredient responsible for effecting said skin change.

**11**. The method according to claim **1**, wherein said method results in skin having a more youthful appearance.

**12**. The method according to any of claims **1–11**, wherein said compound is glycolic acid or a topically effective salt thereof.

**13**. The method according to any of claims **1–11**, wherein said compound is lactic acid in D, L or DL form, or a topically effective salt thereof.

**14**. The method according to any of claims **1–11**, wherein said compound is citric acid or a topically effective salt thereof.

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US005547988B1

# REEXAMINATION CERTIFICATE (3277th)

## United States Patent [19]

Yu et al.

[11] B1 5,547,988

[45] Certificate Issued Jul. 15, 1997

[54] **ALLEVIATING SIGNS OF DERMATOLOGICAL AGING WITH GLYCOLIC ACID, LACTIC ACID OR CITRIC ACID**

[75] Inventors: **Ruey J. Yu**, Ambler; **Eugene J. Van Scott**, Abington, both of Pa.

[73] Assignee: **Tristrata Technology, Inc.**, Wilmington, Del.

**Reexamination Request:**
No. 90/004,435, Oct. 28, 1996

**Reexamination Certificate for:**

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**Related U.S. Application Data**

[63] Continuation of Ser. No. 117,559, Sep. 7, 1993, abandoned, which is a continuation of Ser. No. 936,863, Aug. 27, 1992, abandoned, which is a continuation of Ser. No. 683,437, Apr. 10, 1991, abandoned, which is a continuation-in-part of Ser. No. 469,738, Jan. 19, 1990, abandoned, which is a continuation of Ser. No. 945,680, Dec. 23, 1986, abandoned, and a continuation-in-part of Ser. No. 393,749, Aug. 15, 1989, Pat. No. 5,091,171.

[51] **Int. Cl.**[6] ..... **A61K 7/48**; A61K 31/19

[52] **U.S. Cl.** ..... **514/557**; 514/574; 514/844; 514/847; 514/873

[58] **Field of Search** ..... 514/557, 574, 514/844, 847, 873

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*Primary Examiner*—James J. Seidleck

[57] **ABSTRACT**

Uses of topical compositions comprising a 2-hydroxycarboxylic acid or related compound to alleviate or improve signs of skin, nail and hair changes associated with intrinsic or extrinsic aging are disclosed. 2-Hydroxycarboxylic acids and their related compounds include, for example, 2-hydroxyethanoic acid, 2-hydroxypropanoic acid 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-hydroxybutane-1,4-dioicacid, 2,3-hihydroxybutane-1,4-dioic acid, 2-carboxy 2-hydroxypentane-1,5-dioic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate, ethyl 2-ketopropanoate, and gluconolactone. Topical application of compositions comprising 2-hydroxycarboxylic acid and/or related compounds has been found to alleviate or improve skin lines; blotches; blemishes; nodules; wrinkles; pigmented spots; atrophy; precancerous lesions; elastotic changes characterized by leathery, coarse, rough, dry and yellowish skin; and other skin changes associated with intrinsic aging or skin damages caused by extrinsic factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke and cigarette smoking. Topical applications of such compositions have also been found to improve the overall qualities of nail and hair affected by intrinsic aging or damaged by extrinsic factors.

# REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT



AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1–14** is confirmed.

* * * * *

# EXHIBIT C

US005385938A

# United States Patent [19]

Yu et al.

[11] Patent Number: 5,385,938

[45] Date of Patent: Jan. 31, 1995

[54] **METHOD OF USING GLYCOLIC ACID FOR TREATING WRINKLES**

[76] Inventors: **Ruey J. Yu**, 4 Lindenwold Ave., Ambler, Pa. 19002; **Eugene J. Van Scott**, 3 Hidden La., Abington, Pa. 19001

[21] Appl. No.: **925,877**

[22] Filed: **Aug. 7, 1992**

**Related U.S. Application Data**

[60] Continuation of Ser. No. 840,149, Feb. 24, 1992, abandoned, which is a division of Ser. No. 393,749, Aug. 15, 1989, Pat. No. 5,091,171, which is a continuation-in-part of Ser. No. 945,680, Dec. 23, 1986, abandoned.

[51] **Int. Cl.**[6] ..... **A61K 7/48**; A61K 31/19

[52] **U.S. Cl.** ..... **514/557**; 514/844; 514/847; 514/873

[58] **Field of Search** ..... 514/545, 557, 560, 568, 514/553, 558, 473, 460, 529, 532, 968, 23, 847, 557, 844, 847, 873; 424/401

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[57] **ABSTRACT**

Preventive as well as therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxyacids, alpha ketoacids, related compounds or polymeric forms of hydroxyacids is disclosed. The cosmetic conditions and the dermatologic disorders in which the amphoteric compositions and the polymeric compounds may be useful include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, kyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging, and skin requiring cleansers.

**15 Claims, No Drawings**

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# METHOD OF USING GLYCOLIC ACID FOR TREATING WRINKLES

This application is a continuation of application Ser. No. 07/840,149, filed Feb. 24, 1992, now abandoned, which is a divisional of application Ser. No. 07/393,749, filed Aug. 15, 1989, now U.S. Pat. No. 5,091,171, which is a continuation-in-part application of U.S. application Ser. No. 06/945,680, filed Dec. 23, 1986, now abandoned.

## FIELD OF THE INVENTION

This invention relates generally to therapeutic treatment as well as preventive measures for cosmetic conditions and dermatologic disorders by topical administration of amphoteric compositions or polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds. We initially discovered that alpha hydroxy of keto acids and their derivatives were effective in the topical treatment of disease conditions such as dry skin, ichthyosis, eczema, palmar and plantar hyperkeratoses, dandruff, acne and warts.

We have now discovered that amphoteric compositions and polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds on topical administration are therapeutically effective for various cosmetic conditions and dermatologic disorders.

## BRIEF DESCRIPTION OF THE PRIOR ART

In our prior U.S. Pat. No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoses" we described and claimed the use of certain alpha hydroxyacids, alpha ketoacids and related compounds for topical treatment of-fish-scale like ichthyotic conditions in humans. In our U.S. Pat. No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of these alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis.

In our prior U.S. Pat. No. 4,105,783 entitled "Treatment of Dry Skin" we described and claimed the use of alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dry skin. In our recent U.S. Pat. No. 4,246,261 entitled "Additives Enhancing Topical Corticosteroid Action" we described and claimed that alpha hydroxyacids, alpha ketoacids and their derivatives, could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis and other inflammatory skin conditions.

In our more recent U.S. Pat. No. 4,363,815 entitled "Alpha Hydroxyacids, Alpha Ketoacids and Their Use in Treating Skin Conditions" we described and claimed that alpha hydroxyacids and alpha ketoacids related to or originating from amino acids, whether or not found in proteins, were effective in topical treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier's disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema, pruritus, warts and herpes.

In our most recent patent application Ser. No. 945,680 filed Dec. 23, 1986 and entitled "Additives Enhancing Topical Actions of Therapeutic Agents" we described and claimed that incorporation of an alpha hydroxyacid or related compound can substantially



enhance therapeutic actions of cosmetic and pharmaceutical agents.

## SUMMARY OF THE INVENTION

There is no doubt that alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatment of various cosmetic conditions and dermatologic disorders including dry skin, acne, dandruff, keratoses, age spots, wrinkles, skin lines and disturbed keratinization. However, the compositions containing these acids may irritate human skin on repeated topical applications due to lower pH of the formulations. The irritation may range from a sensation of tingling, itching and burning to clinical signs of redness and peeling. Causes for such irritation may arise from the following:

Upper layers of normal skin have a pH of 4.2 to 5.6, but the compositions containing most alpha hydroxyacids or alpha ketoacids have pH values of less than 3.0. For example, a topical formulation containing 7.6% (1M) glycolic acid has a pH of 1.9, and a composition containing 9% (1M) lactic acid has the same pH of 1.9. These compositions of lower pH on repeated topical applications can cause a drastic pH decrease in the stratum corneum of human skin, and provoke disturbances in intercorneocyte bondings resulting in adverse skin reactions, especially to some individuals with sensitive skin.

Moreover, with today's state of the art it is still very difficult to formulate a lotion, cream or ointment emulsion which contains a free acid form of the alpha hydroxyacid, and which is physically stable as a commercial product for cosmetic or pharmaceutical use.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with a metallic alkali such as sodium hydroxide or potassium hydroxide the composition becomes therapeutically ineffective. The reasons for such loss of therapeutic effects are believed to be as follows:

The intact skin of humans is a very effective barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by oral or other systematic administration, but many of them are much less or totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors; (a) bioavailability of the active ingredient in the topical preparation and (b) percutaneous absorption, penetration and distribution of the active ingredient to the target site in the skin. For example, a topical preparation containing 5% salicylic acid is therapeutically effective as a keratolytic, but that containing 5% sodium salicylate is not an effective product. The reason for such difference is that salicylic acid is in bioavailable form and can penetrate the stratum corneum, but sodium salicylate is not in bioavailable form and cannot penetrate the stratum corneum of the skin.

In the case of alpha hydroxyacids, a topical preparation containing 5% glycolic acid is therapeutically effective for dry skin, but that containing 5% sodium glycollate is not effective. The same is true in case of 5% lactic acid versus 5% sodium lactate. The reason for such difference is that both glycolic acid and lactic acid are in bioavailable forms and can readily penetrate the stratum corneum, but sodium glycollate and sodium lactate are not in bioavailable forms and cannot penetrate the stratum corneum of the skin.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with ammonium hydroxide or an organic base of smaller molecule the composition still shows some therapeutic effects for certain cosmetic conditions such as dry skin, but the composition has lost most of its potency for other dermatologic disorders such as wrinkles, keratoses, age spots and skin changes associated with aging.

It has now been discovered that amphoteric compositions containing alpha hydroxyacids, alpha ketoacids or related compounds, and also the compositions containing dimeric or polymeric forms of hydroxyacids overcomer the aforementioned shortcomings and retain the therapeutic efficacies for cosmetic conditions and dermatologic disorders. The amphoteric composition contains in combination an amphoteric or pseudoamphoteric compound and at least one of the alpha hydroxyacids, alpha ketoacids or related compounds. Such amphoteric system has a suitable pH, and can release the active form of an alpha hydroxyacid or alpha ketoacid into the skin. The dimeric and polymeric forms of alpha, beta or other hydroxyacids in non-aqueous compositions have a more desired pH than that of the monomeric form of the hydroxyacids. The non-aqueous compositions can be formulated and induced to release the active form of hydroxyacids after the compositions have been topically applied to the skin. The cosmetic conditions and dermatologic disorders in humans and animals, in which the amphoteric compositions containing the dimeric or polymeric forms of hydroxyacids may be useful, include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, hyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging and as skin cleansers.

## DETAILED DESCRIPTION OF THE INVENTION

### I. Amphoteric and Pseudoamphoteric Compositions

Amphoteric substances by definition should behave either as an acid or a base, and can be an organic or an inorganic compound. The molecule of an organic amphoteric compound should consist of at least one basic and one acidic group. The basic groups include, for example, amino, imino and guanido groups. The acidic groups include, for example, carboxylic, phosphoric and sulfonic groups. Some examples of organic amphoteric compounds are amino acids, peptides, polypeptides, proteins, creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine and deacetylated chondroitin.

Inorganic amphoteric compounds are certain metallic oxides such as aluminum oxide and zinc oxide.

Pseudoamphoteric compounds are either structurally related to true amphoteric compounds or capable of inducing the same function when they are incorporated into the compositions containing alpha hydroxyacids or ketoacids. Some examples of pseudoamphoteric compounds are creatinine, stearamidoethyl diethylamine, stearamidoethyl diethanolamine, stearamidopropyl dimethylamine, quaternary ammonium hydroxide and quaternium hydroxide.

The amphoteric composition of the instant invention contains in combination an alpha hydroxyacid or alpha ketoacid and an amphoteric or pseudoamphoteric compound. There are two advantages of utilizing an amphoteric or the like compound in the therapeutic composition containing an alpha hydroxy or ketoacid. These are (a) the overall pH of the composition is raised, so that the composition becomes less or non-irritating to the skin and (b) some alpha hydroxy or ketoacid molecules react with the amphoteric compound to form a quadruple ionic complex which acts as buffering system to control the release of alpha hydroxy or ketoacid into the skin, therefore, eliminating the skin irritation and still retaining the therapeutic efficacies.

The following are some examples. 2-Hydroxyethanoic acid (glycolic acid) 1M aqueous solution has pH 1.9. The pHs of compositions change to 3.0 and 3.2 when arginine 0.5M and creatinine 0.5M respectively are incorporated into the formulations. 2-Hydroxypropanoic acid (lactic acid) 1M aqueous solution has pH 1.9. The pHs of compositions change to 3.1 and 6.9 when arginine 0.5M and 1.0M respectively are incorporated into the formulations. 2-Methyl 2-hydroxypropanoic acid (methyllactic acid) 1M aqueous solution has pH 1.9. The pHs of compositions change to 3.3, 3.4 and 3.2 when 0.5M each of arginine, creatinine and 4-aminobutanoic acid respectively are incorporated into the formulations. 2-Hydroxybutane-1,4-dioic acid (malic acid) 1M aqueous solution has pH 1.8, but the pH of the composition changes to 3.0 when creatinine 0.5M is incorporated into the formulation.

Ideally, an amphoteric compound should contain both anionic and cationic groups or functional groups capable of behaving both as an acid and a base. Although inorganic amphoteric compounds such as aluminum oxide, aluminum hydroxide and zinc oxide may be utilized, organic amphoteric compounds have been found to be more efficient in formulating therapeutic compositions of the instant invention.

Organic amphoteric and pseudoamphoteric compounds may be classified into three groups, namely (a) amino acid type, (b) imidazoline and lecithin amphoterics and (c) pseudoamphoterics and miscellaneous amphoterics.

(a) Amino acid type amphoterics. Amphoteric compounds of amino acid type include all the amino acids, dipeptides, polypeptides, proteins and the like which contain at least one of the basic groups such as amino, imino, guanido, imidazolino and imidazolyl, and one of the acidic groups such as carboxylic, sulfonic, sulfinic and sulfate.

Glycine is a simple amphoteric compound which contains only one amino group and one carboxylic group. Lysine contains two amino groups and one carboxylic group. Aspartic acid contains one amino group and two carboxylic groups. Arginine contains one amino group, one guanido group and one carboxylic group. Histidine contains one amino group, one imidazolyl group and one carboxylic group. Taurine contains one amino group and one sulfonic group. Cysteine sulfinic acid contains one amino group, one carboxylic group and one sulfinic group. The amino group of an amphoteric compound may also be substituted, such as in betaine which is a glycine N,N,N-trimethyl inner salt.

Glycylglycine is a simple dipeptide which contains one free amino group and one free carboxylic group. Glycylhistidine is also a dipeptide which contains one free amino group, one imidazolyl group and one free carboxylic group.

The representative amphoteric compounds of amino acid type may be listed as follows: Glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline and proline.

The related amino acids include homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, 3-aminopropanoic acid, theanine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, phenylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β-lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid, 2-methylserine, 3-phenylserine and betaine.

Sulfur-containing amino acids include taurine, cysteinesulfinic acid, methionine sulfoxide and methionine sulfone.

The halogen-containing amino acids include 3,5-diiodotyrosine, thyroxine and monoiodotyrosine. The imino type acids include pipecolic acid, 4-aminopipecolic acid and 4-methylproline.

The dipeptides include for example, glycylglycine, carnosine, anserine, ophidine, homocarnosine, β-alanyllysine, β-alanylarginine. The tripeptides include for example, glutathione, ophthalmic acid and norophthalmic acid. Short-chain polypeptides of animal, plant and bacterial origin containing up to 100 amino acid residues include bradykinin and glucagon. The preferred proteins include for example protamines, histones and other lysine and arginine rich proteins.

(b) Imidazoline and lecithin amphoterics. The amphoteric compounds of imidazoline derived type are commercially synthesized from 2-substituted-2-imidazolines obtained by reacting a fatty acid with an aminoethylethanolamine. These amphoterics include cocoamphoglycine, cocoamphopropionate, and cocoamphopropylsulfonate. The amphoteric compounds of lecithin and related type include for example, phosphatidyl ethanolamine, phosphatidyl serine and sphingomyelin.

(c) Pseudoamphoterics and miscellaneous amphoterics. Many pseudoamphoteric compounds are chemically related or derived from true amphoterics. For example, creatinine is derived from creatine. Other pseudoamphoteric compounds may include fatty amide amines such as stearamidoethyl diethyiamine stearamidoethyl diethanolamine and stearamidopropyl dimethylamine. Other pseudoamphoteric related compounds include quaternary ammonium hydroxide and quaternium hydroxide.

In accordance with the present invention, the alpha hydroxyacid, the alpha ketoacids and the related compounds which are incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders may be classified into three groups.

The first group is organic carboxylic acids in which one hydroxyl group is attached to the alpha carbon of the acids. The generic structure of such alpha hydroxyacids may be represented as follows:

(Ra) (Rb) C (OH) COOH

where Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha hydroxyacids may be present as a free acid or lactone form, or in a salt form with an organic base or an inorganic alkali. The alpha hydroxyacids may exist as stereoisomers as D, L, and DL forms when Ra and Rb are not identical.

Typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc. The alpha hydroxyacids of the first group may be divided into (1) alkyl alpha hydroxyacids, (2) aralkyl and aryl alpha hydroxyacids, (3) polyhydroxy alpha hydroxyacids, and (4) polycarboxylic alpha hydroxyacids. The following are representative alpha hydroxyacids in each subgroup.

(1) Alkyl Alpha Hydroxyacids

1. 2-Hydroxyethanoic acid (Glycolic acid, hydroxyacetic acid) (H) (H) c (OH) COOH
2. 2-Hydroxypropanoic acid (Lactic acid) ($CH_3$) (s) C (OH) COOH
3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid) ($CH_3$) ($CH_3$) C (OH) COOH
4. 2-Hydroxybutanoic acid ($C_2H_5$) (H) C (OH) COOH
5. 2-Hydroxypentanoic acid ($C_3H_7$) (H) C (OH) COOH
6. 2-Hydroxyhexanoic acid ($C_4H_9$) (H) C (OH) COOH
7. 2-Hydroxyheptanoic acid ($C_5H_{11}$ (H) C (OH) COOH
8. 2-Hydroxyoctanoic acid ($C_6H_{13}$) (H) C (OH) COOH
9. 2-Hydroxynonanoic acid ($C_7H_{15}$ ) (H) C (OH) COOH
10. 2-Hydroxydecanoic acid $C_8H_{17}$) (H) C (OH) COOH
11. 2-Hydroxyundecanoic acid ($C_9H_{19}$) (H) C (OH) COOH
12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid) ($C_{10}H_{21}$) (H) C (OH) COOH
13. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid) ($C_{12}H_{25}$) (H) C (OH) COOH
14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid) $C_{14}H_{29}$) (H) C (OH) COOH
15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid) ($C_{16}H_{34}$) (H) C (OH) COOH
16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid) ($C_{18}H_{37}$) (H) C (OH) COOH

(2) Aralkyl And Aryl Alpha Hydroxyacids

1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid) ($C_6H_5$ ) (H) C (OH) COOH
2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid) ($C_6H_5$ ) ($C_6H_5$ ) C (OH) COOH
3. 3 -Phenyl 2-hydroxypropanoic acid (Phenyllactic acid) ($C_6H_5CH_2$) (H) C (OH) COOH
4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid) ($C_6H_5$) ($CH_3$) C (OH) COOH
5. 2-(4′-Hydroxyphenyl)2-hydroxyethanoic acid (4-Hydroxymandelic acid) (HO-$C_6H_4$) (H) C (OH) COOH
6. 2-(4′-Chlorophenyl) 2-hydroxyethanoic acid (4-Chloromandelic acid) (Cl-$C_6H_4$) (H) C (OH) COOH
7. 2-(3′-Hydroxy-4′-methoxyphenyl) 2 -hydroxyethanoic acid (3-Hydroxy-4-methoxymandelic acid) (HO-, $CH_3O$-$C_6H_3$) (H) C (OH) COOH
8. 2-(4′-Hydroxy-3′-methoxyphenyl ) 2-hydroxyethanoic acid (4-Hydroxy-3-methoxymandelic acid) (HO-,$CH_3O$-$C_6H_3$) (H) C (OH) COOH
9. 3-(2′-Hydroxyphenyl)2-hydroxypropanoic acid [3-(2′-Hydroxyphenyl) lactic acid]HO-$C_6H_4$-$CH_2$(H) C (OH) COOH

10. 3-(4'-Hydroxyphenyl) 2 -hydroxypropanoic acid [3-(4'-Hydroxyphenyl) lactic acid]HO-$C_6H_4$-$CH_2$ (H) C (OH) COOH
11. 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid (3,4-Dihydroxymandelic acid) HO-, HO-$C_6H_3$ (H) C (OH) COOH

(3) Polyhydroxy Alpha Hydroxyacids

1. 2,3-Dihydroxypropanoic acid (Glyceric acid) ($HOCH_2$) (H) C (OH) COOH
2. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid) $HOCH_2$ (HO)$CH_2$ (H) C (OH) COOH
3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid) $HOCH_2$ (HO) $CH_2$ (HO) $CH_2$ (H) C (OH) COOH
4. 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid) $HOCH_2$ (HO)$CH_2$ (HO)$CH_2$ (HO)$CH_2$ (H) C (OH) COOH
5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc. ) $HOCH_2$ (HO) $CH_2$ (HO) $CH_2$ (HO) $CH_2$ (HO) $CH_2$ (H) C (OH) COOH

(4) Polycarboxylic Alpha Hydroxyacids

1. 2-Hydroxypropane-1,3-dioic acid (Tartronic acid) HOOC (H) C (OH) COOH
2. 2Hydroxybutane-1,4-dioic acid (Malic acid) HOOC $CH_2$ (H) C (OH) COOH
3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid) HOOC (HO)CH (H) C (OH) COOH
4. 2-Hydroxy-2-carboxypentane-1,5-dioic acid ( Citric acid) HOOC $CH_2$ C (OH) (COOH) $CH_2$ COOH
5. 2, 3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid etc.) HOOC $(CHOH)_4$ COOH

(5) Lactone Forms

The typical lactone forms are gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, and galactoheptonolactone.

The second group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders, is organic carboxylic acids in which the alpha carbon of the acids is in keto form. The generic structure of such alpha ketoacids may be represented as follows:

(Ra) CO COO (Rb)

wherein Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha ketoacids may be present as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc.

In contrast to alpha hydroxyacids the ester form of alpha ketoacids has been found to be therapeutically effective for cosmetic and dermatologic conditions and disorders. For example, while ethyl lactate has a minimal effect, ethyl pyruvate is therapeutically very effective. Although the real mechanism for such difference is not known, we have speculated that the ester form of an alpha ketoacid is chemically and/or biochemically very reactive, and a free acid form of the alpha ketoacid is released in the skin after the topical application.

The representative alpha ketoacids and their esters which may be useful in amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders are listed below:

1. 2-Ketoethanoic acid (Glyoxylic acid) (H) CO COOH
2. Methyl 2-ketoethanoate (H) CO $COOCH_3$
3. 2-Ketopropanoic acid (Pyruvic acid) $CH_3$ CO COOH
4. Methyl 2-ketopropanoate (Methyl pyruvate) $CH_3$ CO $COOCH_3$
5. Ethyl 2-ketopropanoate (Ethyl pyruvate) $CH_3$ CO $COOC_2H_5$
6. Propyl 2-ketopropanoate (Propyl pyruvate) $CH_3$ CO $COOC_3H_7$
7. 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid) $C_6H_5$ CO COOH
8. Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate) $C_6H_5$ CO $COOCH_3$
9. Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate) $C_6H_5$ CO $COOC_2H_5$
10. 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid) $C_6H_5CH_2$ CO COOH
11. Methyl 3 -phenyl -2 -ketopropanoate (Methyl phenylpyruvate) $C_6H_5CH_2$ CO $COOCH_3$
12. Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate) $C_6H_5CH_2$ CO $COOC_2H_5$
13. 2-Ketobutanoic acid $C_2H_5$ CO COOH
14. 2-Ketopentanoic acid $C_3H_7$ CO COOH
15. 2-Ketohexanoic acid $C_4H_9$ CO COOH
16. 2-Ketoheptanoic acid $C_5H_{11}$ CO COOH
17. 2-Ketooctanoic acid $C_6H_{13}$ CO COOH
18. 2-Ketododecanoic acid $C_{10}H_{21}$ CO COOH
19. Methyl 2-ketooctanoate $C_6H_{13}$ CO $COOCH_3$

The third group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic and dermatologic conditions and disorders, is chemically related to alpha hydroxyacids or alpha ketoacids, and can be represented by their names instead of the above two generic structures. The third group of compounds include ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, aleuritic acid and pantoic acid.

II. Dimeric and Polymeric Forms of Hydroxyacids

When two or more molecules of hydroxycarboxylic acids either identical or non-identical compounds are reacted chemically to each other, dimeric or polymeric compounds will be formed. Such dimeric and polymeric compounds may be classified into three groups, namely (a) acyclic ester, (b) cyclic ester and (c) miscellaneous dimer and polymer.

(a) Acyclic ester. The acyclic ester of a hydroxycarboxylic acid may be a dimer or a polymer. The dimer is formed from two molecules of a hydroxycarboxylic acid by reacting the carboxyl group of one molecule with the hydroxy group of a second molecule. For example, glycolyl glycollate is formed from two molecules of glycolic acid by eliminating one mole of water molecule. Likewise, lactyl lactate is formed from two molecules of lactic acid. When two molecules of different hydroxycarboxylic acids are intermolecularly re-

acted, a different dimer is formed. For example, glycolyl lactate is formed by reacting the carboxyl group of lactic acid with the hydroxy group of glycolic acid. The polymer is formed in a similar manner but from more than two molecules of a hydroxycarboxylic acid. For example, glycoly glycoly glycollate is formed from three molecules of glycolic acid. Copolymer is formed from two or more than two different kinds of hydroxycarboxylic acids. For example, glycolyl lactyl glycollate is formed from two molecules of glycolic acid and one molecule of lactic acid.

The acyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

H [-O-C(Ra) (Rb)-CO-]n OH

wherein Ra,Rb=H, alkyl, aralkyl ar aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=1 or any numerical number, with a preferred number of up to 200. Ra and Rb in monomer unit 2, 3, 4 and so on may be the same or the different groups from that in monomer unit 1. For example, Ra,Rb=H in monomer unit 1, and Ra=$CH_3$,Rb=H in monomer unit 2 when n=2 is a dimer called lactyl glycollate, because the first monomer is glycollate unit and the second monomer is lactic acid unit. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms. The dimer and polymer of a hydroxycarboxylic acid may be present as a free acid, ester or salt form with organic base or inorganic alkali.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative acyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolyl glycollate (Glycolic acid glycollate) Ra,Rb=H in units 1 & 2, n=2
2. Lactyl lactate (Lactic acid lactate) Ra=$CH_3$,Rb=H in units 1&2, n=2
3. Mandelyl mandellate Ra=$C_6H_5$,Rb=H in units 1 & 2, n=2
4. Atrolactyl atrolactate Ra=$C_6H_5$,Rb=$CH_3$in units 1 & 2, n=2
5. Phenyllactyl phenyllactate Ra=$C_6H_5CH_2$, Rb=H, in units 1 & 2, n=2
6. Benzilyl benzillate Ra,Rb=$C_6H_5$ in units 1 & 2, n=2
7. Glycolyl lactate Ra=$CH_3$ in unit 1, Ra=H in unit 2, Rb=H in units 1 & 2, n=2
8. Lactyl glycollate Ra=H in unit 1, Ra=$CH_3$ in unit 2, Rb=H in units 1 & 2, n=2
9. Glycolyl glycolyl glycollate Ra,Rb=H in units 1, 2 & 3, n=3
10. Lactyl lactyl lactate Ra=$CH_3$, Rb=H in units 1, 2 & 3, n=3
11. Lactyl glycolyl lactate Ra=$CH_3$ in units 1 & 3, Ra=H in unit 2, Rb=H in units 1, 2 & 3, n=3
12. Glycolyl glycolyl glycolyl glycollate Ra,Rb=H in units 1, 2, 3 & 4, n=4
13. Lactyl lactyl lactyl lactate Ra=$CH_3$, Rb=H in units 1, 2, 3 & 4, n=4
14. Glycolyl lactyl glycolyl lactyl glycollate Ra=H in units 1, 3 & 5, Ra=$CH_3$ in units 2 & 4, Rb=H in units 1, 2, 3, 4 & 5, n=5
15. Polyglycolic acid and polylactic acid

(b) Cyclic ester. The cyclic ester of a hydroxycarboxylic acid may also be a dimer or polymer, the most common type however, is a dimer form. The cyclic dimer may be formed from an identical monomer or different monomers. For example, glycolide is formed from two molecules of glycolic acid by removing two molecules of water, and lactide is formed from two molecules of lactic acid in the same manner. The cyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

[—O—C(Ra) (Rb)—Co—]n

wherein Ra,Rb=H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=1 or any numerical number, however with a preferred number of 2. Ra and Rb in units 1, 2, 3 and so on may be the same or the different groups. For example, in glycolide Ra and Rb are H in both units 1 & 2, but in lactoglycolide Ra is H in unit 1, $CH_3$ in unit 2 and Rb is H in both units 1 & 2. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative cyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolide Ra,Rb=H, n=2
2. Lactide Ra=$CH_3$, Rb=H in units 1 & 2, n=2
3. Mandelide Ra=$C_6H_5$, Rb=H in units 1 & 2, n=2
4. Atrolactide Ra=$C_6H_5$, Rb=$CH_3$ in units 1 & 2, n=2
5. Phenyllactide Ra=$C_6H_5$ $CH_2$, Rb=H in units 1 & 2, n=2
6. Benzilide Ra,Rb=$C_6H_5$ in units 1 & 2, n=2
7. Methyllactide Ra,Rb=$CH_3$ in units 1 & 2, n=2
8. Lactoglycolide Ra=H in unit 1, Ra=$CH_3$ in unit 2 Rb=H in units 1 & 2, n=2
9. Glycolactide Ra=$CH_3$ in unit 1, Ra=H in unit 2 Rb=H in units 1 & 2, n=2

(c) Miscellaneous dimer and polymer. This group includes all the dimeric and polymeric forms of hydroxycarboxylic acids, which can not be represented by any one of the above two generic structures, such as those formed from tropic acid, trethocanic acid and aleuritic acid. When a hydroxycarboxylic acid has more than one hydroxy or carboxy group in the molecule a complex polymer may be formed. Such complex polymer may consist of acyclic as well as cyclic structures.

The following hydroxycarboxylic acids have more than one hydroxy groups: glyceric acid, gluconic acid and gluconolactone, galactonic acid and galactonolactone, glucuronic acid and glucuronolactone, ribonic acid and ribonolactone, galacturonic acid and galacturonolactone, ascorbic acid, gulonic acid and gulonolactone, glucoheptonic acid and glucoheptonolactone. These polyhydroxycarboxylic acids can form complex polymers with themselves or with other simple monohydroxymonocarboxylic acids.

The following hydroxycarboxylic acids have more than one carboxyl groups: malic acid, citric acid, citramalic acid, tartronic acid, agaricic acid and isocitric acid. These monohydroxypolycarboxylic acids can also form complex polymers with themselves or with other simple hydroxycarboxylic acids.

The following hydroxycarboxylic acids have more than one hydroxy and more than one carboxyl groups: tartaric acid, mucic acid and saccharic acid. These polyhydroxypolycarboxylic acids can form even more complex polymers with themselves or with other hydroxycarboxylic acids.

### III. Combination Compositions

Any cosmetic and pharmaceutical agents may be incorporated into amphoteric or pseudoamphoteric compositions, or into compositions containing dimeric or polymeric forms of hydroxyacids with or without amphoteric or pseudoamphoteric systems to enhance therapeutic effects of those cosmetic and pharmaceutical agents to improve cosmetic conditions or to alleviate the symptoms of dermatologic disorder. Cosmetic and pharmaceutical agents include those that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic agents; antiemetics; antimotion sickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidryskin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical cardiovascular agents and other dermatologicals.

Some examples of cosmetic and pharmaceutical agents are clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobenzone, erythromyc in, tetracycline, clindamycin, meclocycline, hydroquinone, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate and vitamin E acetate.

### IV. Specific Compositions For Skin Disorders

We have discovered that topical formulations or compositions containing specific alpha hydroxyacids or alpha ketoacids, or related compounds are therapeutically very effective for certain skin disorders without utilizing any amphoteric or pseudoamphoteric systems. The alpha hydroxyacids and the related compounds include 2-hydroxyethanoic acid, 2 -hydroxypropanoic acid, 2 -methyl 2 -hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid. The alpha ketoacids and their esters include 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate. The mentioned skin disorders include warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

In general, the concentration of the alpha hydroxyacid, the alpha ketoacid or the related compound used in the composition is a full strength to an intermediate strength, therefore the dispensing and the application require special handling and procedures.

If the alpha hdyroxyacid, or the alpha ketoacid or the related compound at full strength (usually 95–100%) is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the liquid compound with or without a gelling agent is directly dispensed as 0.5 to 1 ml aliquots in small vials.

If the alpha hydroxyacid, or the alpha ketoacid or the related compound at full strength is a solid form at room temperature such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid, the solid compound is first dissolved in a minimal amount of vehicle or vehicle system such as water, or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 g, and the 70% strength solution thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, 0.5 to 3% of for example, hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose or carbomer may be incorporated into the above solution.

To prepare an intermediate strength (usually 20–50%), the alpha hydroxyacid, alpha ketoacid or related compound either a liquid or solid form at room temperature is first dissolved in a vehicle or vehicle system such as water, acetone, ethanol, propylene glycol and butane 1,3-diol. For example, 2-hydroxyethanoic acid or 2-ketopropanoic acid 30 g is dissolved in ethanol 56 g and propylene glycol 14 g, and the 30% strength solution thus obtained is dispensed as 7 to 14 ml aliquots in dropper bottles.

For topical treatment of warts, keratoses, age spots, acne, nail infections, wrinkles or aging related skin changes, patients are advised to apply a small drop of the medication with a toothpick or a fine-caliber, commonly available artist's camel hair brush to affected lesions only and not surrounding skin. Prescribed applications have been 1 to 6 times daily for keratoses and ordinary warts of the hands, fingers, palms, and soles. For age spots, acne, nail infections, wrinkles and aging related skin changes topical applications have been 1 to 2 times daily.

Very often, frequency and duration of applications have been modified according to clinical responses and reactions of the lesions and the patient or responsible family member is instructed accordingly. For example, some clinical manifestations other than pain have been used as a signal to interrupt application. These manifestations include distinct blanching of the lesions or distinct peripheral erythema.

Alternatively, an office procedure may be adapted when a full strength of 2-ketopropanoic acid or 70% 2-hydroxyethanoic acid is used for topical treatment of age spots, keratoses, acne, warts or facial wrinkles.

We have found that the above mentioned alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatments of warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

Preparation of the Therapeutic compositions

Amphoteric and pseudoamphoteric compositions of the instant invention may be formulated as solution, gel, lotion, cream, ointment, shampoo, spray, stick, powder or other cosmetic and pharmaceutical preparations.

To prepare an amphoteric or pseudoamphoteric composition in solution form at least one of the aforementioned amphoteric or pseudoamphoteric compounds and in combination at least one of the hydroxyacids or the related compounds are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone or other pharmaceutically acceptable vehicle. The concentration of the amphoteric or pseudoamphoteric compound may range from 0.01 to 10M, the preferred concentration ranges from 0.1 to 3M. The concentration of hydroxyacids or the related compounds may range from 0.02 to 12M, the preferred concentration ranges from 0.2 to 5M.

In the preparation of an amphoteric or pseudoamphoteric composition in lotion, cream or ointment form, at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are initially dissolved in a solvent such as water, ethanol and/or propylene glycol. The solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment base such as hydrophilic ointment or petrolatum. The concentrations of amphoteric or pseudoamphoteric compounds and hydroxyacids used in the compositions are the same as described above.

Amphoteric and pseudoamphoteric compositions of the instant invention may also be formulated in a gel form. A typical gel composition of the instant invention utilizes at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are dissolved in a mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as methyl cellulose, ethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

Since dimeric and polymeric forms of hydroxyacids are less stable in the presence of water or the like vehicle, cosmetic and pharmaceutical compositions should be prepared as anhydrous formulations. Typical vehicles suitable for such formulations include mineral oil, petrolatum, isopropyl myristate, isopropyl palmitate, diisopropyl adipate, octyl palmitate, acetone, squalene, squalane, silicone oils, vegetable oils and the like. Therapeutic compositions containing dimeric or polymeric forms of hydroxyacids do not require any incorporation of an amphoteric or pseudoamphoteric compound. The concentration of the dimeric or polymeric form of a hydroxyacid used in the composition may range from 0.1 to 100%, the preferred concentration ranges from 1 to 40%. Therapeutic compositions may be formulated as anhydrous solution, lotion, ointment, spray, powder or the like.

To prepare a combination composition in a pharmaceutically acceptable vehicle, a cosmetic or pharmaceutical agent is incorporated into any one of the above composition by dissolving or mixing the agent into the formulation.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limited. therefore, any of the aforementioned amphoteric or pseudoamphoteric compounds, hydroxyacids, dimeric or polymeric forms of hydroxyacids may be substituted according to the teachings of this invention in the following examples.

EXAMPLE 1

An amphoteric composition containing 1M 2-hydroxyethanoic acid and 0.5M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxyethanoic acid (glycolic acid) 7.6 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. An amphoteric composition formulated from 1M 2-hydroxyethanoic acid and 1M L-arginine has pH 6.3. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 2

An amphoteric composition containing 1M 2-hydroxyethanoic acid and 0.5M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.3.

EXAMPLE 3

An amphoteric composition containing 1M 2-hydroxyethanoic acid and 0.5M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.1.

EXAMPLE 4

A pseudoamphoteric composition containing 1M 2-hydroxyethanoic acid and 0.5M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.0 when 1M instead of 0.5M creatinine is incorporated into the formulation.

EXAMPLE 5

An amphoteric composition containing 1M 2-hydroxyethanoic acid and 0.5M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

## EXAMPLE 6

An amphoteric composition containing 0.5M 2-hydroxyethanoic acid and 0.5M dipeptide of β-Ala-L-His for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and L-carnosine (β-alanyl-L-histidine) 11.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.5.

## EXAMPLE 7

An amphoteric composition containing 0.5M 2-hydroxyethanoic acid and 0.5M cycloleucine for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and 1-aminocyclopentane-1-carboxylic acid (cycloleucine) 6.5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

## EXAMPLE 8

A pseudoamphoteric composition containing 0.5M 2-hydroxyethanoic acid and 0.25M 1,12-diaminododecane for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and 1.12-diaminododecane 5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

## EXAMPLE 9

An amphoteric composition containing 0.5M 2-hydroxyethanoic acid and 5% protamine for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and protamine 5 g, isolated and purified from salmon sperm are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

## EXAMPLE 10

An amphoteric composition containing 1M 2-hydroxypropanoic acid and 0.5M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxypropanoic acid (DL-lactic acid) USP grade 9.0 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. An amphoteric composition formulated from 1M 2-hydroxypropanoic acid and 1M L-arginine has pH 6.9. The solution has pH 1.9 if no amphoteric compound is incorporated.

## EXAMPLE 11

An amphoteric composition containing 1M 2-hydroxypropanoic acid and 0.5M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.6. An amphoteric composition formulated from 1M 2-hydroxypropanoic acid and 1M L-lysine has pH 8.4

## EXAMPLE 12

An amphoteric composition containing 1M 2-hydroxypropanoic acid and 0.5M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0

## EXAMPLE 13

A pseudoamphoteric composition containing 1M 2-hydroxypropanoic acid and 0.5M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.3. The composition has pH 4.4 when 1M instead of 0.5M creatinine is incorporated into the formulation.

## EXAMPLE 14

An amphoteric composition containing 1M 2-hydroxypropanoic acid and 1M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-histidine 15.5 g are dissolved in 35 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated as pH 4.9.

## EXAMPLE 15

An amphoteric composition containing 1M 2-hydroxypropanoic acid and 1M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and glycylglycine 13.2 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0.

## EXAMPLE 16

An amphoteric composition containing 1M 2-methyl-2-hydroxypropanoic acid and 0.5M L-arginine in solu-

tion form for dandruff or dry skin may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid (methyllactic acid) 10.4 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. An amphoteric composition formulated from 1M 2-methyl-2-hydroxypropanoic acid and 1M L-arginine has pH 6.5. The solution has pH 1.9 if no amphoteric compound is incorporated.

## EXAMPLE 17

An amphoteric composition containing 1M 2-methyl-2-hydroxypropanoic acid and 0.5M 4-aminobutanoic acid in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and 4-aminobutanoic acid 5.2 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

## EXAMPLE 18

An amphoteric composition containing 1M 2-methyl-2-hydroxypropanoic acid and 1M dipeptide of Gly-Gly in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and glycylglycine 13.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

## EXAMPLE 19

A pseudoamphoteric composition containing 1M 2-methyl-2-hydroxypropanoic acid and 0.5M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4. The composition has pH 4.4 when 1M instead of 0.5M creatinine is incorporated into the formulation.

## EXAMPLE 20

An amphoteric composition containing 0.5M 2-phenyl-2-hydroxyethanoic acid and 0.5M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid (mandelic acid) 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 5.0. The composition has pH 2.2 if no amphoteric compound is incorporated.

## EXAMPLE 21

An amphoteric composition containing 0.5M 2-phenyl-2-hydroxyethanoic acid and 0.5M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 25 ml of water. The solution thus obtained is mixed with an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated for pH 4.6.

## EXAMPLE 22

A pseudoamphoteric composition containing 0.5M 2-phenyl 2-hydroxyethanoic acid and 0.5M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and creatinine 5.7 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 4.6.

## EXAMPLE 23

An amphoteric composition containing 0.5M 2-phenyl 2-hydroxyethanoic acid and 0.5M L-citrulline for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-citrulline 8.8 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

## EXAMPLE 24

An amphoteric composition containing 1M citric acid and 1M L-arginine for cosmetic conditions and dermatologic disorders may be formulated as follows.

Citric acid 19.2 g is dissolved in water 50 ml and propylene glycol 10 ml. L-Arginine 17.4 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.8 if no amphoteric compound is incorporated.

## EXAMPLE 25

A pseudoamphoteric composition containing 1M citric acid and 1M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

Citric acid 19.2 g and creatinine 11.3 g are dissolved in 40 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.7.

## EXAMPLE 26

An amphoteric composition containing 1M malic acid and 1M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxybutanedioic acid (DL-malic acid) 13.4 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 27

A pseudoamphoteric composition containing 1M malic acid and 0.5M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Malic acid 13.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.0. The composition has pH 3.8 when 1M instead of 0.5M creatinine is incorporated into the formulation.

EXAMPLE 28

An amphoteric composition containing 1M tartaric acid and 1M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

2,3-Dihydroxybutanedioic acid (DL-tartaric acid) 15.9 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.7 if no amphoteric compound is incorporated.

EXAMPLE 29

A pseudoamphoteric composition containing 1M tartaric acid and 1M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Tartaric acid 15.0 g and creatinine 11.3 g are dissolved in 35 ml of water. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4.

EXAMPLE 30

An amphoteric composition containing 1M gluconolactone 0.5M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and L-arginine 8.7 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. The composition has pH 5.9 when 1M instead of 0.5M L-arginine is incorporated into the formulation. If no amphoteric compound is incorporated the pH of the composition is 1.8.

EXAMPLE 31

An amphoteric composition containing 1M gluconolactone and 0.5M 4-aminobutanoic acid for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and 4-aminobutanoic acid 5.2 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals ave been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 32

An amphoteric composition containing 1M gluconolactone and 1M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and glycylglycine 13.2 g are dissolved in water 50 ml and propylene glycol 5 ml. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1

EXAMPLE 33

A pseudoamphoteric composition containing 1M gluconolactone and 0.5M creatinine for cosmetic conditions and dermatologic disorders may be formulated as follows.

Gluconolactone 17.8 g and creatinine 5.7 g are dissolved in water 60 ml and propylene glycol 10 ml. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.8 when 1M instead of 0.5M creatinine is incorporated into the formulation.

EXAMPLE 34

A pseudoamphoteric composition containing 1M pyruvic acid and 1M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

2-Ketopropanoic acid (pyruvic acid) 8.8 g and creatinine 11.3 g are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.4.

EXAMPLE 35

An amphoteric composition containing 0.5M benzilic acid and 0.5M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2,2-Diphenyl 2-hydroxyethanoic acid (benzilic acid) 11.4 g and L-lysine 7.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9. The composition has pH 2.7 if no amphoteric compound is incorporated.

EXAMPLE 36

An amphoteric composition containing 0.5M benzilic acid and 0.5M L-histidine for cosmetic and dermatologic conditions may be formulated as follows.

Benzilic acid 11.4 g and L-histidine 7.8 g are dissolved in water 40 ml and propylene glycol 20 ml. Ethyl cellulose 2 g is added with stirring, and sufficient amount of ethanol is added to make a total volume of the gel to 100 ml. The amphoteric gel composition thus formulated has pH 5.0.

EXAMPLE 37

A pseudoamphoteric composition containing 0.5M benzilic acid and 0.5M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

Benzilic acid 11.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. Sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.9.

EXAMPLE 38

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxyethanoic acid and 0.05%

betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Betamethasone dipropionate 1% in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

## EXAMPLE 39

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxyethanoic acid and 0.05% clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1% in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

## EXAMPLE 40

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxyethanoic acid and 0.1% triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

## EXAMPLE 41

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxyethanoic acid and 0.2% 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol: water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

## EXAMPLE 42

A pseudoamphoteric composition containing in combination 0 5M 2-hydroxypropanoic acid and 0.05% betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of a oil-in-water emulsion. Betamethasone dipropionate 1% in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

## EXAMPLE 43

A pseudoamphoteric composition containing in combination 0.5M hydroxypropanoic acid and 0.05% clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1% in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

## EXAMPLE 44

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxypropanoic acid and 0.1% triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

## EXAMPLE 45

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxypropanoic acid and 0.2% 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol:water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

## EXAMPLE 46

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxyethanoic acid and 2% clotrimazole in a cream form for athlete's foot and other fungal infections may be formulated as follows. 2-Hydroxyethanoic acid 3.8 g, clotimazole 2 g and creatinine 5.7 g are dissolved in water 20 ml and propylene glycol 5 ml, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

## EXAMPLE 47

A pseudoamphoteric composition containing in combination 0.5M 2 -hydroxyethanoic acid and 2% erythromycin in solution form for ache may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, erythromycin 2 g and creatinine 5.7 g are dissolved in water 25 ml, ethanol ml and propylene glycol 15 ml. More water is then added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

## EXAMPLE 48

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxyethanoic acid and 1%

ketoconazole in a cream form for fungal infections may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, ketoconazole 1 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

## EXAMPLE 49

A pseudoamphoteric composition containing in combination 0.5M 2 -hydroxypropanoic acid and 2% clotrimazole in a cream form for fungal infections may be formulated as follows.

2-Hydroxypropanoic acid 3.8 g, clotrimazole 2 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 4.1.

## EXAMPLE 50

A pseudoamphoteric composition containing in combination 0.5M 2-hydroxyethanoic acid and 2% tetracycline in a gel form for dermatologic disorders may be formulated as follows.

2 -Hydroxyethanoic acid 3.8 g, tetracycline 2 g, creatinine 5.7 g, xantham gum 0.2 g, carbomer-941 1 g, propylene glycol 5 ml, ethanol 20 ml and enough amount of water are homogenized to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated for acne and oily skin has pH 4.2.

## EXAMPLE 51

An amphoteric composition containing 0.2M aleuritic acid and 0.1M L-lysine in a solution form for cosmetic and dermatologic conditions may be formulated as follows.

Aleuritic acid 6.1 g and L-lysine 1.5 g are dissolved in sufficient amount of a solution from ethanol:propylene glycol 80:20 to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 6.4.

## EXAMPLE 52

A typical composition containing a dimeric form of alpha hydroxyacid in solution for acne, dandruff, and as a skin cleanser may be formulated as follows.

Glycolide powder 1.0 g is dissolved in ethanol 89 ml and propylene glycol 10 ml. The composition thus formulated has pH 4.0, and contains 1% active ingredient.

## EXAMPLE 53

A typical composition containing a dimeric form of alpha hdyroxyacid in ointment for dry skin, psoriasis, eczema, pruritus, wrinkles and other skin changes associated with aging may be formulated as follows.

Glycolide powder 2.0 g is mixed uniformly with petrolatum 66 g and mineral oil 32 g. The composition thus formulated contains 2% active ingredient.

## EXAMPLE 54

A typical composition containing a full strength or a high concentration of an alpha hydroxyacid, alpha ketoacid or closely related compound for topical treatments of warts, keratoses, acne, age spots, nail infections, wrinkles and aging related skin changes may be prepared as follows.

If the alpha hydroxyacid, alpha ketoacid or closely related compound at full strength is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the compound is directly dispensed as 0.5 to 1 ml aliquots in small vials. If the compound is a solid form at room temperature such as 2-hydroxyethanoic acid and 2-methyl 2-hydroxypropanoic acid, it is first dissolved in minimal amount of an appropriate solvent or solvent system such as water or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 ml, and the 70% strength 2-hydroxyethanoic acid thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, methyl cellulose or hydroxyethyl cellulose 1 g may be added to the above solution.

## EXAMPLE 55

A typical composition containing an intermediate strength of an alpha hydroxyacid, alpha ketoacid or closely related compound for topical treatment of warts, keratoses, acne, nail infections, age spots, wrinkles and aging related skin changes may be prepared as follows.

2-Hydroxyethanoic acid or 2-ketopropanoic acid 40 g is dissovled in ethanol 54 g and propylene glycol 6 g, and the 40% strength solution thus obtained is dispensed as 5 to 10 ml aliquots in dropper bottles.

## TEST RESULTS

In order to determine whether amphoteric and pseudoamphoteric compositions of the instant invention were therapeutically effective for various cosmetic conditions and dermatologic disorders, a total of more than 90 volunteers and patients participated in these studies. Some participating subjects were given two preparations; an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound, and a vehicle placebo. Others were given multiple preparations containing a known pharmaceutical agent such as a corticosteroid with or without incorporation of an amphoteric or pseudoamphoteric composition consisting of an alpha hydroxyacid or the related compound of the instant invention. The amphoteric and pseudoamphoteric compositions were formulated according to the Examples described in the previous section.

### 1. Common dry skin.

Human subjects having ordinary dry skin or with moderate degrees of dry skin as evidenced by dryness, flaking and cracking of the skin were instructed to apply topically the lotion, cream or ointment containing an alpha hydroxyacid or the related compound in amphoteric or pseudoamphoteric composition, on the affected area of the skin. Topical application, two to three times daily, was continued for two to four weeks.

In all the 28 subjects tested, the feeling of the skin dryness disappeared within a week of topical application. The rough and cracked skin became less pronounced and the skin appeared normal and felt smooth after several days of topical treatment. The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective when incorporated into the amphoteric or pseudoamphoteric compositions for dry skin are as follows:

2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropanoic acid (lactic acid), 2-methyl-2-hydroxypropanoic acid (methyllactic acid), phenyl 2-hydroxyethanoic acid (mandelic acid), phenyl 2-methyl-2-hydroxyethanoic acid (atrolactic acid), 3-phenyl-2-hydroxypropanoic acid (phenyllactic acid), diphenyl 2-hydroxyethanoic acid (benzilic acid), gluconolactone, tartaric acid, citric acid, saccharic acid, malic acid, tropic acid, glucuronic acid, galacturonic acid, gluconic acid, 3-hydroxybutanoic acid, quinic acid, ribonolactone, glucuronolactone, galactonolactone, pyruvic acid, methyl pyruvate, ethyl pyruvate, phenylpyruvic acid, benzoylformic acid and methyl benzoylformate.

The ordinary dry skin conditions, once restored to normal appearing skin, remained improved for some time until causes of dry skin, such as low humidity, cold weather, excessive contact pressure, detergents, soaps, solvents, chemicals, etc., again caused recurrence of the dry skin condition. On continued use it was also found that twice daily topical application of an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound of the instant invention prevented the development of new dry skin lesions.

2. Severe dry skin.

In severe dry skin, the skin lesions are different from the ordinary dry skin. A main cause of severe dry skin is inherited genetic defects of the skin. The involved skin is hyperplastic, fissured and has thick adherent scales. The degree of thickening is such that lesions are palpably and visually elevated. The thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These two attributes of thickness and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows:

| | DEGREE OF IMPROVEMENT | | | | |
|---|---|---|---|---|---|
| | None (0) | Mild (1+) | Moderate (2+) | Substantial (3+) | Complete (4+) |
| Thickness | Highly elevated | Detectable reduction | Readily apparent reduction | Barely elevated | Normal thickness |
| Texture | Visibly rough | Palpably rough | Uneven but not rough | Slightly uneven | Visibly and palpably smooth |

By means of such parameters, degrees of change in lesions can be numerically recorded and comparisons made of one treated site to another.

In order to evaluate the amphoteric and pseudoamphoteric compositions of the instant invention, a total of 6 patients having severe dry skin conditions were treated with the compositions containing an alpha hydroxyacid or the related compound.

Tested areas were of a size convenient for topical applications, i.e., circles 5 cm in diameter demarcated with a plastic ring of that size inked on a stamp pad. The medicinal lotions or creams were topically applied by the patient in an amount sufficient to cover the treatment sites. Applications were made three times daily and without occlusive dressings. Applications were discontinued at any time when resolutions of the lesion on the treatment area was clinically judged to be complete.

The test results of amphoteric and pseudoamphoteric compositions containing the following alpha hydroxyacids or the related compounds on patients with severe dry skin are summarized as follows:

4+Effectiveness; glycolic acid, lactic acid, methyllactic acid, mandelic acid, tropic acid, atrolactic acid and pyruvic acid.

3+Effectiveness; benzilic acid, gluconolactone, malic acid, tartaric acid, citric acid, saccharic acid, methyl pyruvate, ethyl pyruvate, phenyllactic acid, phenylpyruvic acid, glucuronic acid and 3-hydroxybutanoic acid.

2+Effectiveness; mucic acid, ribonolactone, 2-hydroxydodecanoic acid, quinic acid, benzoylformic acid and methyl benzoylformate.

3. Psoriasis.

The involved skin in psoriasis is hyperplastic (thickened), erythematous (red or inflamed), and has thick adherent scales. The degree of thickening is such that lesions are elevated up to 1 mm above the surface of adjacent normal skin; erythema is usually an intense red: the thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These three attributes of thickness, color and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows.

| | DEGREE OF IMPROVEMENT | | | | |
|---|---|---|---|---|---|
| | None (0) | Mild (1+) | Moderate (2+) | Substantial (3+) | Complete (4+) |
| THICKNESS | Highly elevated | Detectable reduction | Readily apparent reduction | Barely elevated | Normal thickness |
| TEXTURE | Visibly rough | Palpably rough | Uneven but not rough | Slightly uneven | Visibly and palpably smooth |
| COLOR | Intense Red | Red | Dark Pink | Light Pink | Normal Skin Color: |

By means of such parameters, degree of improvement in psoriatic lesions can be numerically recorded and comparisons made of one treated site to another.

Patients having psoriasis participated in this study. Amphoteric and pseudoamphoteric compositions containing both an alpha hdyroxyacid or the related compound and a corticosteroid were prepared according to

the Examples. Compositions containing only a corticosteroid were also prepared and included in the comparison test. Test areas were kept to minimal size convenient for topical application, i.e., circles approximately 4 cm in diameter. The medicinal compositions were topically applied by the patient in an amount (usually about 0.1 milliliter) sufficient to cover the test site. Applications were made two to three times daily and without occlusive dressings. Test periods usually lasted for two to four weeks. The test results on patients having psoriasis are summarized on the following table.

Topical Effects on Psoriasis of Antipsoriatic Compositions

| Compositions* | Therapeutic Effectiveness |
|---|---|
| Hydrocortisone 2.5% alone | 1+ |
| With lactic acid | 2+ |
| With glycolic acid | 2+ |
| With ethyl pyruvate | 2+ |
| With methyl pyruvate | 2+ |
| With benzilic acid | 2+ |
| With pyruvic acid | 2+ |
| With methyllactic acid | 2+ |
| Hydrocortisone 17-valerate 0.2% alone | 2+ |
| With lactic acid | 3+ |
| With glycolic acid | 3+ |
| With benzilic acid | 3+ |
| With ethyl pyruvate | 3+ |
| With methyl pyruvate | 3+ |
| With gluconolactone | 3+ |
| With pyruvic acid | 3+ |
| Betamethasone dipropionate 0.05% alone | 3+ |
| With lactic acid | 4+ |
| With glycolic acid | 4+ |
| With ethyl pyruvate | 4+ |
| With methyl pyruvate | 4+ |
| With mandelic acid | 4+ |
| With benzilic acid | 4+ |
| Clobetasol propionate 0.05% alone | 3+ |
| With lactic acid | 4+ |
| With glycolic acid | 4+ |
| With ethyl pyruvate | 4+ |
| With methyl pyruvate | 4+ |
| With methyllactic acid | 4+ |
| With mandelic acid | 4+ |
| With tropic acid | 4+ |
| With benzilic acid | 4+ |

*Except the "alone" preparations, all others were amphoteric or pseudoamphoteric compositions containing 0.2 to 2M alpha hydroxyacids or related compounds.

We have also found that an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound in combination with an antimetabolite agent such as 5-fluorouracil with or without additional incorporation of a corticosteroid is therapeutically effective for topical treatment of psoriasis.

4. Eczema.

In a topical treatment of eczema patients, hydrocortisone alone at 2.5% or hydrocortisone 17-valerate alone at 0.2% would achieve only 2+ improvement, and betamethasone dipropionate or clobetasol propionate alone at 0.05% would achieve only a 3+improvement on all the eczema patients tested. Test results of amphoteric and pseudoamphoteric compositions containing both a corticosteroid and one of the following alpha hydroxyacids or the related compounds are shown as follows:

3+Effectiveness; hydrocortisone 2.5% or hydrocortisone 17-valerate 0.2% plus lactic acid, glycolic acid, mandelic acid, ethyl pyruvate, gluconolactone, benzilic acid or ribonolactone.

4+Effectiveness; betamethasone dipropionate or clobetasol propionate 0.05% plus lactic acid, glycolic acid, mandelic acid, ethyl pyruvate, methyl pyruvate, benzilic acid, gluconolactone, citric acid, tartaric acid or methyllactic acid.

5. Oily Skin and Skin Cleanse.

Human subjects having oily skin or blemished skin as well as acne patients having extremely oily skin participated in this study. Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds were formulated in solution or gel form.

Each participating subject received a solution or a gel preparation containing an alpha hydroxyacid or a related compound in an amphoteric or pseudoamphoteric composition. The participating subjects were instructed to apply topically the solution or gel medication on the affected areas of forehead or other part of the face. Three times daily applications were continued for 2 to 6 weeks.

The degree of improvement of oily skin as well as the rate of improvement of acne lesions were clinically evaluated. Most participants reported that oiliness of skin disappeared within one to two weeks of topical administration, and the skin so treated became smooth and soft. Many participating subjects preferred gel preparations than solution compositions. It was found that all the participants showed substantial improvements on oily skin and acne lesions by six weeks of topical administration of amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds of the instant invention.

Those alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for oily skin and as skin cleansers include: benzilic acid, glycolic acid, lactic acid, methyllactic acid, mandelic acid, pyruvic acid, ethyl pyruvate, methyl pyruvate, tropic acid, malic acid, gluconolactone, 3-hydroxybutanoic acid, glycolide and polyglycolic acid. As a skin cleanser for oily skin or acne-prone skin, the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound may also be incorporated with other dermatologic agents. For example, an amphoteric gel composition may consist of both an alpha hydroxyacid and erythromycin or tetracycline.

6. Acne

Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds of the instant invention in a solution or gel form were provided to patients having comedongenic and/or papulopustular lesions of acne. Each participating patient was instructed to apply topically the composition on the involved areas of the skin such as forehead, face and chest. Three times daily administration was continued for 6 to 12 weeks.

The degree and rate of improvement on acne lesions were clinically evaluated. It was found that acne lesions consisting mainly of comedones improved substantially after 6 to 8 weeks of topical administration with the amphoteric or the pseudoamphoteric composition containing an alpha hydroxyacid or the related compound. The time for complete clearing of comedongenic acne treated with the amphoteric or pseudoamphoteric composition of the instant invention varied from 6 to 12 weeks.

As a topical treatment for papulopustular and/or pustular acne the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound may incorporate in addition an antiacne agent. The antiacne agents include antibiotics such as erythromycin, tetracycline, clindamycin, meclocycline and minocycline, and retinoids such as retinoic acid. Such combination compositions have been found to be therapeutically more effective for topical treatment of severe acne.

7. Age Spots

Many small and large discolored lesions, commonly called age spots on the face and the back of the hands are benign keratoses, if they are not variants of actinic keratoses. Very few of such age spots are true lentigines, therefore alpha hydroxyacids and the related compounds may be effective in eradicating most age spots without concurrent use of skin bleaching agents such as hydroquinone and monobenzone. However, additional beneficial effects have been found when a skin bleaching agent such as hydroquinone or monobenzone is also incorporated into the compositions of the instant invention for age spots involving pigmented lesions.

Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds, with or without incorporation of hydroquinone were provided to volunteer subjects and patients having age spot keratoses, melasma, lentigines and/or other pigmented lesions. Each participating subject received two products, i.e., with or without the addition of 2% hydroquinone to the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound.

The volunteer subjects and patients were instructed to apply topically one medication on one side of the body such as left side of the face or on the back of the left hand, and the other medication on the other side of the body such as on right side of the face or on the back of the right hand. Specific instructions were given to the participating subjects that the medications were applied three times daily to the lesions of age spot keratoses, melasmas, lentigines and/or other pigmented lesions. Clinical photos were taken of participating subjects before the initiation of the topical treatment and every 4 weeks during the course of treatment.

At the end of 4 to 8 weeks, improvement of age spot keratoses was clinically discernible. After 4 to 6 months of topical treatment, substantial improvement of age spot keratoses occurred in the majority of subjects tested. Complete eradication of age spot keratoses occurred after 6 to 9 months of topical administration with the amphoteric or pseudoamphoteric compositions of the instant inventions.

Amphoteric or pseudoamphoteric compositions containing both an alpha hydroxyacid or the related compound and hydroquinone were judged to be more effective in eradicating pigmented age spots, melasma, lentigines and other pigmented lesions.

The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for age spots with or without combination with hydroquinone include glycolic acid, lactic acid, methyllactic acid, mandelic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, benzilic acid, gluconolactone, malic acid, tartaric acid, citric acid and tropic acid. For flat or slightly elevated seborrheic keratoses on the face and/or the back of the body, amphoteric or pseudoamphoteric compositions containing higher concentrations of alpha hydroxyacids or the related compounds have been found to be effective in eradicating such lesions.

Actinic keratoses may be successfully treated with amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds in combination with an antimetabolite agent such as 5-fluorouracil.

8. Warts.

Eradications of common warts by topical application of amphoteric or pseudoamphoteric compositions require higher than usual concentrations of alpha hydroxyacids or the related compounds in the formulations. The amphoteric or pseudoamphoteric compositions were formulated as a liquid or light gel form, and dispensed usually as 0.5–1 ml aliquots in small vials.

Topical applications were made discreetly to wart lesions by adult patients or by responsible adult family members. For ordinary usual warts of hands, fingers, palms and soles topical applications were made 2 to 4 times daily, and were continued for 2 to 6 weeks. Generally, the overlying stratum corneum of the wart lesion change in appearance after several weeks topical application of the composition. In most cases, the wart lesion simply fell off. The skin then healed normally without forming any scars.

We have also found that when a dermatologic agent such as 5-fluorouracil is incorporated into the amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds, the medications have been very effective for topical treatment of warts without using higher concentrations of alpha hydroxyacids or the related compounds.

The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for topical treatment of warts with or without incorporation of 5-fluorouracil include glycolic acid, lactic acid, pyruvic acid, ethyl pyruvate, methyl pyruvate and mandelic acid.

Topical formulations and compositions containing specific alpha hydroxyacids, alpha ketoacids or the related compounds at full strengths or high to intermediate concentrations prepared according to Examples 54 and 55, without utilizing amphoteric or pseudoamphoteric systems, have also been tested for ordinary warts of the hands, fingers, palms and soles. Participating patients have been advised to apply a small drop of the medication with a toothpick or a fine caliber brush to the center of a wart lesion only. Prescirbed applications have been 3 to 6 times daily, and are continued until the patient feels pain.

For the more rough-surfaced wart, the duration of application has been as short as one or a few days. For lesions with more compact, less permeable stratum corneum, the time to experience gpain has been longer. Frequency and duration of applications have been modified according to other clinical responses and reactions of lesions, and the patient or responsible family member is instructed accordingly.

For example, some clinical manifestations other than pain have also been used as a signal to interrupt application. These manifestations have included distinct blanching of the lesions or distinct peripheral erythema. Very often, discomfort is the usual signal of clinical reactions.

Generally, the overlying stratum corneum of the wart lesions became loose, and the whole wart lesion

simply fell off. The skin then healed normally without forming any scars.

9. Athlete's Foot and Nail Infections

Amphoteric and pseudoamphoteric compositions containing both an antifungal agent and one of the alpha hydroxyacids or the related compounds were provided to patients having frequent recurrence of fungal infections involving the foot. The antifungal agents include clotrimazole, miconazole, ketoconazole and griseofulvin. When both feet but not toe nails were involved in the infection, the patients were instructed to apply topically the compositions of the instant invention on the left foot, and a brand-name antifungal product on the right foot. Three times daily applications were continued for one to four weeks. The degree and rate of improvement on skin lesions were clinically evaluated, and comparison was made one side of the body against the other. It was found that the skin lesions improved much faster with the amphoteric or pseudoamphoteric compositions containing both the antifungal agent and the alpha hydroxyacid or the related compound. The alpha hydroxyacids or the related compounds seemed to enhance the efficacies of the antifungal agents, and also to eliminate the discomforts such as itching, tingling, burning and irritation due to fungal infections. When toe nails were not involved the infected skin generally healed within one to two weeks from topical application of the amphoteric or pseudoamphoteric composition containing both an antifungal agent and an alpha hydroxyacid or the related compound.

Fungal infections of the nails are very difficult to treat, because antifungal products to date are not therapeutically effective for topical treatment of nails. One of the reasons is that most antifungal drugs have not been formulated as bioavailable forms in the commercial products. When tow nails were involved in the infections, patients were provided with amphoteric or pseudoamphoteric compositions containing in combination an antifungal agent and an alpha hydroxyacid or an alpha ketoacid at higher concentrations ranging from 20 to 99%, dispensed as 1–2 ml aliquots in small vials. The patients were instructed to apply topically the compositions discreetly to the infected nail surface by means of a fine calibre paint brush. the technique was the same as for application of nail polish, that is careful avoidance of contact with lateral nail folds or any peri-ungual skin. Once or twice daily applications were continued for 2 to 8 weeks.

As mentioned above, while brand-name antifungal products are usually not effective against fungus infections within or underneath the nail, it was found that the amphoteric or pseudoamphoteric compositions containing an antifungal agent and an alpha hydroxyacid or alpha ketoacid were therapeutically effective in eradicating fungal infections of the nails. Such treatment may cause in some instances the treated nail plate to become loose and eventually fell off from the nail bed. This happened quite naturally without any feeling of pain nor bleeding, and the skin lesion healed quickly with normal growth of a new nail.

10. Wrinkles

Wrinkles of skin may be due to natural aging and/or sun damage. Most fine wrinkles on the face are due to natural or innate aging, while coarse wrinkles on the face are the consequence of actinic or sun damage. Although the real mechanism of wrinkles formation in the skin is still unknown, it has been shown that visible fine wrinkles are due to diminution in the number and diameter of elastic fibers in the papillary dermis, and also due to atrophy of dermis as well as reduction in subcutaneous adipose tissue. Histopathology and electron microscopy studies indicate that coarse wrinkles are due to excessive deposition of abnormal elastic materials in the upper dermis and thickening of the skin. At present there are no commercial products which have been found to be therapeutically effective for topical eradication of wrinkles, although retinoic acid (tretinoin) has been shown to be beneficial for sun damaged skin.

In order to determine whether the amphoteric or pseudoamphoteric composition containing the alpha hydroxyacids, alpha ketoacids or the related compounds are therapeutically effective for wrinkles, patients and volunteer subjects participated in this study. The participants were instructed to apply the formulations of the instant invention twice daily on areas of facial wrinkles for 4 to 12 months. All participants were told to avoid sun exposure, and to use sunscreen products if exposure to sunlight was unavoidable. Photographs of each side of the face for each participant were taken at the beginning of the study and repeated at one to three-month intervals. The participants were asked not to wear any facial make-up at the time of each office visit. Standardized photographic conditions were used including the use of same lot of photographic film, the same light source at two feet from the face, aimed at a locus on the frontal aspect of each cheek. Each time photographs were taken with camera aimed perpendicular to the cheek. At the end of study twenty two participants had been entered into the study for at least four months. Clinical evaluations and review of photographs have revealed substantial reductions in facial wrinkles of the temporal region and cheek area on at least one side of the face in eighteen cases. Degree of improvement and reduction in wrinkles has been evaluated and determined to be mild to moderate in six participants but very substantial in twelve participants.

The alpha hydroxyacids, alpha ketoacids and other related compounds including their lactone forms which may be incorporated into the amphoteric and pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders such as dry skin, acne, age spots, keratoses, warts and skin wrinkles or in combination with other dermatologic agents to enhance therapeutic effects include the following:

(1 ) Alkyl Alpha Hydroxyacids

2-Hydroxyethanoic acid (Glycolic acid), 2-Hydroxypropanoic acid (Lactic acid), 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid), 2-Hydroxybutanoic acid, 2-Hydroxypentanoic acid, 2-Hydroxyhexanoic acid, 2-Hydroxyheptanoic acid, 2-Hydroxyoctanoic acid, 2-Hydroxynonanoic acid, 2-Hydroxydecanoic acid, 2-Hydroxyundecanoic acid, 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid), 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid), 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid), 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid), 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid).

(2) Aralkyl And Aryl Alpha Hydroxyacids

2-Phenyl 2-hydroxyethanoic acid (Mandelic acid), 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid),

3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid), 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Atrolactic acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Clorophenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid, 3-(4'-Hydroxyphenyl) 2-hydroxypropanoic acid, 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid.

(3) Polyhydroxy Alpha Hydroxyacids

2,3-Dihydroxypropanoic acid (Glyceric acid), 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid), 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid), 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; aldonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid), 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid, etc.)

(4) Polycarboxylic Alpha Hydroxyacids

2-Hydroxypropane-1,3-dioic acid (Tartronic acid), 2-Hydroxybutane-1,4-dioic acid (Malic acid), 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid), 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid), 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid, etc.)

(5) Alpha Hydroxyacid Related Compounds

Ascorbic acid, quinic acid, isocitric acid, tropic acid, 3-chlorolactic acid, trethocanic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid and aleuritic acid.

(6) Alpha Ketoacids And Related Compounds

2-Ketoethanoic acid (Glyoxylic acid), Methyl 2-ketoethanoate, 2 -Ketopropanoic acid (Pyruvic acid), Methyl 2-ketopropanoate (Methyl pyruvate), Ethyl, 2-ketopropanoate (Ethyl pyruvate), Propyl 2-ketopropanoate (Propyl pyruvate), 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid), Methyl 2-phenyl-2-ketoethanoate (MEthyl benzoylformate), Ethyl 2-Phenyl-2-ketoethanoate (Ethyl benzoylformate), 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid), Methyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate), 2-Ketobutanoic acid, 2-Ketopentanoic acid, 2-Ketohexanoic acid, 2-Ketoheptanoic acid, 2-Ketooctanoic acid, 2-Ketododecanoic acid, Methyl 2-ketooctanoate

The amphoteric and pseudoamphoteric compounds which may be incorporated into the compositions of the instant invention for cosmetic and dermatologic conditions include amino acids, peptides, polypeptides, proteins and the like compounds such as creatinine and creatine.

The dimeric and polymeric forms of alpha hydroxyacids and the related comopounds which may be incorporated into the compositions of the instant invention include acyclic esters and cyclic ester; for example, glycolyl glycollate, lactyl lactate, glycolide, lactide, polyglycolic acid and polylactic acid.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims and all changes which come within the meaning and equivalency of the claims are therefore intended to be embraced therein.

We claim:

**1**. Method of visibly reducing a human skin wrinkle comprising topically applying to said wrinkle a composition comprising 2-hydroxyethanoic acid (glycolic acid), or a topically effective salt thereof, in an amount and for a period of time sufficient to visibly reduce said wrinkle, wherein said wrinkle is a facial wrinkle.

**2**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid is in the form of a free acid.

**3**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid is in salt form with an organic base useful in topical preparations.

**4**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid is in salt form with a nonmetallic inorganic alkali useful in topical preparations.

**5**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid or topically effective salt thereof is applied periodically for a period of time sufficient to achieve at least a visibly mild to moderate reduction of said wrinkle.

**6**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid or topically effective salt thereof is applied periodically for a period of time sufficient to achieve at least a substantial reduction of said wrinkle.

**7**. The method according to claim **1**, wherein said period of time is at least two months.

**8**. The method according to claim **1**, wherein said period of time is at least three months.

**9**. The method according to claim **1**, wherein said period of time is at least four months.

**10**. The method according to claim **1**, wherein said topical application is on a daily basis.

**11**. The method according to claim **1**, wherein said wrinkle is a fine wrinkle.

**12**. The method according to claim **1**, wherein said wrinkle is a coarse wrinkle.

**13**. The method according to claim **1**, wherein said wrinkle is the result of actinic or sun damage.

**14**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid or topically effective salt thereof is present in a topically acceptable composition comprising a carrier.

**15**. The method according to claim **14**, wherein said composition is a lotion, cream, gel, ointment or solution.

* * * * *

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# REEXAMINATION CERTIFICATE (3269th)

United States Patent [19] [11] B1 5,385,938

Yu et al. [45] Certificate Issued Jul. 15, 1997

[54] **METHOD OF USING GLYCOLIC ACID FOR TREATING WRINKLES**

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[60] Continuation of Ser. No. 840,149, Feb. 24, 1992, abandoned, which is a division of Ser. No. 393,749, Aug. 15, 1989, Pat. No. 5,091,171, which is a continuation-in-part of Ser. No. 945,680, Dec. 23, 1986, abandoned.

[51] **Int. Cl.**[6] ..... **A61K 31/19**; A61K 7/48

[52] **U.S. Cl.** ..... **514/557**; 514/844; 514/847; 514/873

[58] **Field of Search** ..... 514/557, 844, 514/847, 873

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*Primary Examiner*—James J. Seidleck

[57] **ABSTRACT**

Preventive as well as therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxyacids, alpha ketoacids, related compounds or polymeric forms of hydroxyacids is disclosed. The cosmetic conditions and the dermatologic disorders in which the amphoteric compositions and the polymeric compounds may be useful include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, kyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging, and skin requiring cleansers.

1

# REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT

2

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1–15** is confirmed.

* * * * *

# EXHIBIT D

US005389677A

# United States Patent [19]

Yu et al.

[11] Patent Number: 5,389,677

[45] Date of Patent: * Feb. 14, 1995

[54] **METHOD OF TREATING WRINKLES USING GLYCALIC ACID**

[76] Inventors: **Ruey J. Yu**, 4 Lindenwold Ave., Ambler, Pa. 19002; **Eugene J. Van Scott**, 3 Hidden La., Abington, Pa. 19001

[ * ] Notice: The portion of the term of this patent subsequent to Feb. 25, 2009 has been disclaimed.

[21] Appl. No.: **89,101**

[22] Filed: **Jul. 12, 1993**

**Related U.S. Application Data**

[60] Division of Ser. No. 8,223, Jan. 22, 1993, which is a continuation of Ser. No. 812,858, Dec. 23, 1991, abandoned, which is a continuation of Ser. No. 469,738, Jan. 19, 1990, abandoned, which is a continuation of Ser. No. 945,680, Dec. 23, 1986, abandoned.

[51] **Int. Cl.**[6] ..... **A61K 7/48**; A61K 31/19

[52] **U.S. Cl.** ..... **514/557**; 514/844; 514/847; 514/873

[58] **Field of Search** ..... 514/857, 844, 847, 873

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*Primary Examiner*—Mukund J. Shah
*Assistant Examiner*—Philip I. Datlow
*Attorney, Agent, or Firm*—Foley & Lardner

[57] **ABSTRACT**

Composition and method for enhancing therapeutic effects of topically applied agents are disclosed. The cosmetic or therapeutic composition may include one or more of cosmetic or pharmaceutical agents present in a total amount of from **0.01** to **40** percent and one or more of hydroxycarboxylic acids or related compounds present in a total amount of from **0.01** to **99** percent by weight of the total composition. The cosmetic and pharmaceutical agents may include but not limited to age spots, wrinkles and keratoses removing agents; vitamins; aloes; sun screens; tanning, depigmenting and shampooing agents; antiyeasts; antifungal, antibacterial and antiviral agents; topical bronchial dilators and topical cardiovascular agents; hormonal agents; vasodilators; retinoids and other dermatological agents. The hydroxycarboxylic acids and related compounds include organic alpha and beta hydroxycarboxylic acids, alpha and beta ketocarboxylic acids and salts thereof. Topical application of the cosmetic or therapeutic composition has been found to achieve a substantial increase in cosmetic or therapeutic effect of the active ingredient in humans and domesticated animals.

**10 Claims, No Drawings**

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# METHOD OF TREATING WRINKLES USING GLYCALIC ACID

This application is a division of application Ser. No. 08/008,223, filed Jan. 22, 1993, which is a continuation of application Ser. No. 07/812,858, filed Dec. 23, 1991, (now abandoned), which is a continuation of application Ser. No. 07/469,738, filed Jan. 19, 1990, (now abandoned), which is a continuation of application Ser. No. 06/945,680, filed Dec. 23, 1986, (now abandoned).

This invention relates generally to method and composition containing hydroxyacid or related compound for enhancing therapeutic effects of cosmetic or pharmaceutical agent. As will be subsequently described in detail, we initially discovered that alpha hydroxy or keto acids and their derivatives were effective in the topical treatment of disease conditions such as dry skin, ichthyosis, eczema, palmar and plantar hyperkeratoses, dandruff, acne and warts.

We have now discovered that hydroxyacids or related compounds wherein incorporated into a therapeutic composition can substantially enhance topical effects of cosmetic and pharmaceutical agents.

In our prior U.S. Pat. No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoes" we described and claimed the use of certain alpha hydroxy acids, alpha keto acids and related compounds for topical treatment of fish-scale like ichthyotic conditions in humans. In our U.S. Pat. No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of these certain alpha hydroxy acids, alpha keto acids and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis.

In our prior U.S. Pat. No. 4,105,783 entitled "Treatment of Dry Skin: we described and claimed the use of alpha hydroxy acids, alpha keto acids and their derivatives for topical treatment of dry skin. In our recent U.S. Pat. No. 4,246,261 entitled "Additives Enhancing Topical Corticosteroid Action" we described and claimed that alpha hydroxy acids, alpha keto acids and their derivatives, in small amounts could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis and other inflammatory skin conditions.

In our more recent U.S. Pat. No. 4,363,815 entitled "Alpha Hydroxy acids, Alpha Keto acids and Their Use in Treating Skin Conditions: we described and claimed that alpaca hydroxy acids and alpha keto acids related to or originating from amino acids, whether or not found in proteins, were effective in topical treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier's disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema, pruritus and possibly warts and herpes.

In our most recent U.S. Pat. No. 4,518,789 entitled "Phenyl Alpha-Acyloxyacetamide Derivatives and Their Therapeutic Use" we described and claimed that phenyl alpha acyloxyacetamide derivatives in topical or systemic administration were useful and effective for pruritus, atopic dermatitis, eczema, psoriasis, acne, dry skin, dandruff, malodors of integumental areas, various aches, pains and discomforts of skin, joints and other body parts in humans and domestic animals.

The intact skin of humans is a very effective barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by systemic administration, but many of them are much less or totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors a) Percutaneous absorption and penetration b) Bioavailability of the penetrated pharmaceutical agent to the target site in the skin. To be therapeutically effective as a topical agent a pharmaceutical drug must penetrate the stratum corneum into the epidermal layers, distributed and bioavailable to the target sites for pharmacologic action. Many pharmacologic agents can readily penetrate the skin but they are not bioavailable to the target sites in the skin, therefore therapeutic effect is minimal and ineffective.



It has now been discovered that hydroxyacids and related compounds including those described or not described in our previous patents and additional compounds can substantially enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders or other afflictions. Cosmetic and pharmaceutical agents may include any chemical substances natural or synthetic, intended for topical application to the skin or its appendages in human and animals. Some examples of cosmetic and pharmaceutical agents include age spots and keratoses removing agents, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirants, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringents, softeners, emollient agents, coal tar, bath oils, sulfur, rinse conditioners, foot care agents, fungicides, hair growth promoters, hair removers, keratolytic agents, moisturizer agents, powder, shampoos, skin bleaches, skin protectants, soaps, cleansers, antiaging agents, sunscreen agents, wart removers, wet dressings, vitamins, tanning agents, topical antihistamin agents, hormones, vasodilators, retinoids, bronchial dilators, topical cardiovascular agents and other dermatologicals.

The enhancing compounds of the instant invention are hydroxycarboxylic acids and related compounds. There are three groups of such hydroxyacids. The first is hydroxymonocarboxylic acids having the following chemical structure:

$$R_1\,(CR_2OH)_m(CH_2)_n\,COOH$$

wherein

$R_1$, $R_2$ =H, alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having 1 to 25 carbon atoms.

m=1, 2, 3, 4, 5, 6, 7, 8 or 9

n=0 or a numerical number up to 23

When n=0 and m=1 or more, the hydroxymonocarboxylic acid is also called aldonic acid. The name comes from a carbohydrate, aldose, which may be oxidized to aldonic acid by the oxidation of the aldehyde group in aldose to the carboyxlic group.

The hydroxymonocarboxylic acid may be present as a free acid, lactone, or salt form. The lactone form could be either inter or intramolecular lactone, however, most common ones are intramolecular lactones with a ring structure formed by elimination of one or more water molecules between a hydroxy group and the carboxylic group. Since the hydroxymonocarboxy-

lic acids are organic in nature, they may form a salt or a complex with an inorganic or organic base such as ammonium hydroxide, sodium or potassium hydroxide, or triethanolamine.

The hydroxymonocarboxylic acid and its related compounds may also exist as stereoisomers such as D, L, and DL forms.

The typical alkyl, aralkyl and aryl groups for $R_1$ and $R_2$ include methyl, ethyl, propyl, isopropyl, benzyl and phenyl. The hydrogen atoms of the $R_1$ and $R_2$ and $(CH_2)_n$ may be substituted by a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy, saturated or unsaturated, having 1 to 9 carbon atoms. Representative hydroxymonocarboxylic acids are listed below:

1. 2-Hydroxyacetic acid (Glycolic acid) $R_1=H$, $R_2=H$, $m=1$, $n=0$
2. 2-Hydroxypropanoic acid (Lactic acid) $R_1=CH_3$, $R_2=H$, $m=1$, $n=0$
3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid) $R_1=CH_3$, $R_2=CH_3$, $m=1$, $n=0$
4. 2-Hydroxybutanoic acid $R_1=C_2H_5$, $R_2=H$, $m=1$, $n=0$
5. Phenyl 2-hydroxyacetic acid (Mandelic acid) $R_1=C_6H_5$, $R_2=H$, $m=1$, $n=0$
6. Phenyl 2-methyl 2-hydroxyacetic acid (Atrolactic acid) $R_1=C_6H_5$, $R_2=CH_3$, $m=1$, $n=0$
7. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid) $R_1=C_6H_5$, $R_2=H$, $m=1$, $n=1$
8. 2,3-Dihydroxypropanoic acid (Glyceric acid) $R_1=H$, $R_2=H$, $m=2$, $n=0$
9. 2, 3, 4-Trihydroxybutanoic acid $R_1=H$, $R_2=H$, $m=3$, $n=0$
10. 2, 3, 4, 5-Tetrahydroxypentanoic acid $R_1=H$, $R_2=H$, $m=4$, $n=0$
11. 2, 3, 4, 5, 6-Pentahydroxyhenxanoic acid $R_1=H$, $R_2=H$, $m=5$, $n=0$
12. 2-Hydroxydodecanoic acid (alpha hydroxylauric acid) $R_1=C_{10}H_{21}$, $R_2=H$, $m=1$, $n=0$
13. 2, 3, 4, 5, 6, 7-Hexahydroxyheptanoic acid $R_1=H$, $R_2=H$, $m=6$, $n=0$
14. Diphenyl 2-hydroxyacetic acid (benzilic acid) $R_1=C_6H_5$, $R_2=C_6H_5$, $m=1$, $n=0$
15. 4-Hydroxymandelic acid $R_1=C_6H_4(OH)$, $R_2=H$, $m=1$, $n=0$
16. 4-Chloromandelic acid $R_1=C_6H_4(Cl)$, $R_2=H$, $m=1$, $n=0$
17. 3-Hydroxybutanoic acid $R_1=CH_3$, $R_2=H$, $m=1$, $n=1$
18. 4-Hydroxybutanoic acid $R_1=H$, $R_2=H$, $m=a$, $n=2$
19. 2-Hydroxyhexanoic acid $R_1=C_4H_9$, $R_2=H$, $m=1$, $n=0$
20. 5-Hydroxydodecanoic acid $R_1=C_7H_{15}$, $R_2=H$, $m=1$, $n=3$
21. 12-Hydroxydodecanoic acid $R_1=H$, $R_2=H$, $m=1$, $n=10$
22. 10-Hydroxydecanoic acid $R_1=H$, $R_2=H$, $m=1$, $n=8$
23. 16-Hydroxyhexadecanoic acid $R_1=H$, $R_2=H$, $m=1$, $n=14$
24. 2-Hydroxy-3-methylbutanoic acid $R_1=C_3H_7$, $R_2=H$, $m=1$, $n=0$
25. 2-Hydroxy-4-methylpentanoic acid $R_1=C_4H_9$, $R_2=H$, $m=1$, $n=0$
26. 3-Hydroxy-4-methoxymandelic acid $R_1=C_6H_3(OH)(OCH_3)$, $R_2=H$, $m=1$, $n=0$
27. 4-Hydroxy-3-methoxymandelic acid $R_1=C_6H_3(OH)(OCH_3)$, $R_2=H$, $m=1$, $n=0$
28. 2-Hydroxy-2-methylbutanoic acid $R_1=C_2H_5$, $R_2=CH_3$, $m=1$, $n=0$
29. 3-(2-Hydroxyphenyl) lactic acid $R_1=C_6H_4(OH)CH_2$, $R_2=H$, $m=1$, $n=0$
30. 3-(4-Hydroxyphenyl) lactic acid $R_1=C_6H_4(OH)CH_2$, $R_2=H$, $m=1$, $n=0$
31. Hexahydromandelic acid $R_1=C_6H_{11}$, $R_2=H$, $m=1$, $n=0$
32. 3-Hydroxy-3-methylpentanoic acid $R_1=C_2H_5$, $R_2=CH_3$, $m=1$, $n=1$
33. 4-Hydroxydecanoic acid $R_1=C_6H_{13}$, $R_2=H$, $m=1$, $n=2$
34. 5-Hydroxydecanoic acid $R_1=C_5H_{11}$, $R_2=H$, $m=1$, $n=3$
35. Aleuritic acid $R_1=C_6H_{12}(OH)$, $R_2=H$, $m=2$, $n=7$

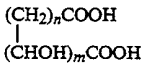
The linear lactic acid polymer is an intermolecular lactone formed by elimination of one water molecule between the hydroxy group of one molecule of lactic acid and the carboxylic group of a second molecule of lactic acid. The common linear lactic acid polymer may contain 3 lactic acid units.

Ribonic acid is one of the stereoisomers of 2, 3, 4, 5-tetrahydroxypentanoic acid, and the corresponding lactone is ribonolactone. Gluconic acid, galactonic acid, gulonic acid and mannonic acid are typical 2, 3, 4, 5, 6-pentahydroxyhexanoic acids and their corresponding lactones are gluconolactone, galactonolactone, gulonolactone and mannonolactone respectively. The related compounds of hydroxymonocarboxylic acids are ketomonocarboxylic acids which are formed from the former by a oxidation reaction or in vivo by a dehydrogenase enzyme. For example, 2-ketopropanoic acid (pyruvic acid) and 2-hydroxypropanoic acid (lactic acid) are converted to each other in vivo by the enzyme, lactate dehydrogenase. Although pure pyruvic acid (liquid form) can be kept in a refrigerator for an extended period of time a composition containing pyruvic acid for topical use is not very stable at an elevated temperature. Therefore, for practical purposes pyruvic acid esters are used instead.

The representative esters are methyl pyruvate, ethyl pyruvate, propyl pyruvate and isopropyl pyruvate. Other representative ketomonocarboxylic acids and their esters are phenyl pyruvic acid and its esters such as methyl phenyl pyruvate, ethyl phenyl pyruvate and propyl phenyl pyruvate; formyl formic acid (2-ketoacetic acid) and its esters such as methyl, ethyl and propyl formyl formate; benzoyl formic acid and its esters such as methyl, ethyl and propyl benzoyl formate; 4-hydroxybenzoylformic acid and its esters; 4-hydroxyphenylpyruvic acid and its esters; 2-hydroxyphenylpyruvic acid and its esters.

Many hydroxy or ketomonocarboxylic acids are structurally related to amino acids either naturally occurring in proteins or not. For example alaninc and pyruvic acid are interconverted to each other in vivo by an enzyme alanine dehydrogenase or alanine ketoglutarate transaminase. As mentioned earlier pyruvic acid and lactic acid are interconverted to each other in vivo by the enzyme lactate dehydrogenase. Therefore, alanine, pyruvic acid and lactic acid are chemically related in that the amino group of alanine may be converted to the keto group of pyruvic acid or the hydroxy group of lactic acid. The same relationships may apply to formyl formic acid and glycolic acid to glycine; hydroxpyruvic acid and glyceric acid to serine; phenyl pyruvic acid and phenyl lactic acid to phenylalanine; 2-keto- and 2-hydroxy-4 (methylthio) butanoic acids to methionine.

The second kind of hydroxyacid is hydroxydicarboxylic acid having the following chemical structure:



wherein

m=1, 2, 3, 4, 5, 6, 7, 8 or 9

n=0 or a numerical number up to 23

The hydroxydicarboxylic acid may also be present as a free acid, lactone or salt form. The lactone form could be either inter or intramolecular lactone. However, the common lactone is an intramolecular lactone with a ring structure formed by elimination of one or more water molecule between a hydroxy group and one of the carboxylic groups. Since the hydroxydicarboxylic acid is organic in nature, it may form a salt or a complex with an inorganic or organic base such as ammonium hydroxide. sodium or potassium hydroxide, or triethanolamine.

The hydroxydicarboxylic acid and its related compounds may also exist as stereoisomers such as D, L, DL and meso forms.

The hydrogen atom attached to the carbon atom may be substituted by a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy of saturated or unsaturated, having 1 to 9 carbon atoms.

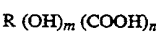
When n=0 and m=1 or more, the hydroxydicarboxylic acid is also called aldaric acid. The name comes from the carbohydrate, and the common ones are saccharic acid and galactaric acid. Representative hydroxydicarboxylic acids are listed below:

1. 2-Hydroxypropanedioic acid (Tartronic acid) m=1, n=0
2. 2-Hydroxybutanedioic acid (Malic acid) m=1, n=1
3. Erythraric acid and Threaric acid (Tartaric acid) m=2, n=0
4. Arabiraric acid, Ribaric acid, Xylaric acid and Lyxaric acid m=3, n=0
5. Glucaric acid (saccharic acid), Galactaric acid (Mucic acid), Mannario acid, Gularic acid, Allaric acid, Altraric acid, Idaric acid and Talaric acid m=4, n=0

Commercially available saccharolactone (D-saccharic acid 1, 4-lactone) is an intramolecular lactone formed by elimination of one water molecule between the hydroxy group at position 4 and the carboxylic group at position 1.

The third type of hydroxyacid is a miscellaneous group of compounds which is not readily represented by the above generic structure of either the first type or the second type. Included in the third type of hydroxyacids are the following:

Hydroxycarboxylic acid of



Wherein m,n=1,2,3,4,5,6,7,8, or 9

R=H, alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having 1 to 25 carbon atoms.

citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, ascorbic acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

The third type of hydroxyacid may also be present as a free acid, lactone or salt form. The lactone form could be either an inter or intramolecular lactone, however, most common are intramolecular lactones with a ring structure. Commonly known glucuronolactone is a r-lactone i.e. 1,4-lactone of intramolecular type.

The hydroxyacid of the third type may also exist as stereoisomers such as D, L, DL and meso forms. The hydrogen atom attached to the carbon atom may be substituted by a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy of saturated or unsaturated, having 1 to 9 carbon atoms.

Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the percutaneous penetration or the therapeutic efficacy of cosmetic and pharmaceutical agents. The cosmetic and pharmaceutical agents may include but not limited to: age spots and keratoses removing agents, vitamins, aloes, retinoids, sun screens; tanning, depigmenting and shampooing agents; antiperspirants, antiyeasts, antifungal, antibacterial and antiviral agents; topical bronchial dilators; topical cardiovascular agents; keratoses, age spots and wrinkles removal agents, hair growth promoting agents and other dermatological agents.

Hydroxyacids and related compounds may also be used alone in the prophylactic and therapeutic treatment of cosmetic conditions or dermatologic disorders characterized by disturbed keratinization, aging, lipid metabolism or inflammation. The representative hydroxyacids are listed below:

citramalic acid, tropic acid, benzilic acid, ribonic acid and ribonolactone, gulonic acid and gulonolactone, 2,3,4-trihydroxybutanoic acid, 2,3,4,5-tetrahydroxypentanoic acid, 2,3,4,5,6-pentahydroxyhexanoic acid, 2-hydroxylauric acid, 2,3,4,5,6,7-hexahydroxyheptanoic acid, aleuritic acid, 4-hydroxymandelic acid, 4-chloromandelic acid, 2-hydroxy-3-methylbutanoic acid, 2-hydroxy-4-methylpentanoic acid, 3-hydroxy-3-methylbutanoic acid, 2-hydroxy-4-methylpentanoic acid, 3-hydroxy-4-methoxymandelic acid, 4-hydroxy-3-methoxymandelic acid, 3-(2-hydroxyphenyl) lactic acid, 3-(4-hydroxyphenyl) lactic acid, hexahydromandelic acid, 3-hydroxy-3-methylpentanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 4-hydroxybutanoic acid, 2-hydroxyhexanoic acid, 5-hydroxylauric acid, 12-hydroxylauric acid, 10-hydroxydecanoic acid, 16-hydroxyhexadecanoic acid, 4-hydroxydecanoic acid, 5-hydroxydecanoic acid, and 4-hydroxy-2, 2-diphenylbutanoic acid.

Preparation of the Therapeutic Compositions

To prepare a therapeutic composition in solution form at least one of the aforementioned enhancing compounds of hydroxyacids and a cosmetic or pharmaceutical agent are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone or other pharmaceutically acceptable vehicles. The concentration of hydroxyacids may range from 0.01 to 99 percent by weight of the total composition. The concentration

of the cosmetic or pharmaceutical agent ranges from 0.01 to 40 percent by weight of the total composition.

In the preparation of a therapeutic composition in cream or ointment form at least one of hydroxyacids and one of cosmetic or pharmaceutic agents are initially dissolved in a solvent such as water, ethanol, acetone, propylene glycol or polysorbate 80. the solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment base such as hydrophilic ointment or petrolatum. The concentrations of hydroxyacids, cosmetic and pharmaceutical agents may range from 0.01 to 99 percent by weight of the total composition.

Therapeutic compositions of the instant invention may also be formulated in gel, lotion, shampoo, spray, stick or powder. A typical gel composition of the instant invention utilizes at least one of hydroxyacids and one of cosmetic or pharmaceutical agents dissolved in a mixture of ethanol, wafer and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limitative. Therefore, any of the aforementioned hydroxyacids, cosmetic and pharmaceutical agents may be substituted according to the teachings of this invention in the following examples.

## EXAMPLE 1

A prophylactic and therapeutic composition in solution form for age spots and for keratoses may be prepared as follows.

Malic acid 1 gram, gluconolactone 19 grams and citric acid 0.5 gram are dissolved in a mixture of ethanol 30 ml, water 42 ml and glycerin 5 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The hydroxyacids, malic acid, gluconolactone and citric acid have been added a) as antioxidants to help stabilize the hydroquinone in the composition b) to enhance the penetration and the efficacy of hydroquinone c) to normalize the disturbed keratinization in age spot and keratoses.

The composition thus formulated contains 2% hydroquinone, 1% malic acid, 19% gluconolactone, 0.5% citric acid, and has pH 3.3

## EXAMPLE 2

A therapeutic composition in solution form for age spots and for keratoses may be formulated as follows.

Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The composition thus formulated contains 2% hydroquinone, 2% citric acid, 20% methyllactic acid, and has pH 3.6.

## EXAMPLE 3

A prophylactic and therapeutic composition containing minoxidil and lactic acid for hair growth and for prevention of hair loss on the scalp may be formulated as follows.

Minoxidil 2 grams and lactic acid 3 ml are dissolved in a mixture of ethanol 80 ml and propylene glycol 15 ml with stirring until a clear solution is obtained. The composition thus formulated contains 2% minoxidil, 3% lactic acid, and has pH 4.7. The lactic acid has been added to help minoxidil dissolved into solution, to enhance the penetration and the efficacy of minoxidil for hair growth.

## EXAMPLE 4

A prophylactic and therapeutic composition in solution form for hair growth on the scalp may be formulated as follows.

Minoxidil 2 grams and ethyl pyruvate 2 ml are dissolved in a mixture of ethanol 80 ml and propylene glycol 16 ml. The composition thus formulated contains 2% minoxidil, 2% ethyl pyruvate, and has pH 5.0. The ketoacid ester, ethyl pyruvate has been added to enhance the penetration and the efficacy of minoxidil for hair growth on the scalp.

## EXAMPLE 5

A therapeutic composition containing anthralin and hydroxyacid for psoriasis may be formulated as follows.

Anthralin powder 0.5 gram and alpha hydroxyisobutyric acid 4 grams are dissolved in a mixture of ethanol 50 ml, acetone 30 ml and diisopropyl adipate 16 ml with stirring until a clear yellowish solution is obtained. The composition thus formulated contains 0.5% anthralin, 4% alpha hydroxyisobutyric acid, and has pH 4.2. The hydroxyacid has been added to enhance the penetration and the efficacy of anthralin for psoriasis.

## EXAMPLE 6

A therapeutic composition containing thionicotinamide and hydroxyacid for psoriasis, keratoses and warts may be formulated as follows.

Thionicotinamide 2 grams and lactic acid 20 ml are dissolved in a mixture of ethanol 40 ml, water 30 ml and propylene glycol 8 ml with stirring until a clear yellowish solution is obtained. The composition thus formulated contains 2% thionicotinamide, 20% lactic acid, and has pH 3.3. The lactic acid has been added to enhance the penetration and the efficacy of thionicotinamide, and also to normalize the disturbed keratinization in psoriasis, keratoses and warts.

## EXAMPLE 7

A therapeutic composition containing 6-aminonicotinamide and hydroxyacid for psoriasis, keratoses and warts may be formulated as follows.

6-Aminonicotinamide 1 gram and glycolic acid 19 grams are dissolved in a mixture of ethanol 40 ml, water 32 ml and propylene glycol 8 ml with stirring until a clear solution is obtained. The composition thus formulated contains 1% 6-aminonicotinamide, 19% glycolic acid, and has pH 3.0. The glycolic acid has been added to enhance the penetration and the efficacy of 6-Aminonicotinamide, and also to normalize the disturbed keratinization in psoriasis, keratoses and warts.

EXAMPLE 8

A therapeutic composition containing clotrimazole and hydroxyacid for fungal infection may be formulated as follows.

Clotrimazole 1 gram and lactic acid 4 ml are dissolved in 4 ml of ethanol, and the solution thus obtained is mixed with 91 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 1% clotrimazole, 4% lactic acid, and has pH 3.2. The lactic acid has been added to enhance the penetration and the efficacy of clotrimazole for athlete's foot, and also to speed up healing and normalize the disturbed keratinization.

EXAMPLE 9

A prophylactic and therapeutic composition containing chlorhexidine and hydroxyacid as general antiseptics on skin, and for prophylactic and therapeutic treatment of acne may be formulated as follows. Chlorhexidine diacetate 1 gram and benzilic acid 5 grams are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 14 ml with stirring until a clear solution is obtained. The composition thus formulated contains 1% chlorhexidine, 5% benzilic acid, and has pH 4.4. Benzilic acid has been added to enhance the antibacterial effect of chlorhexidine, to eliminate the oiliness of the skin, and to improve the acne lesions.

EXAMPLE 10

A prophylactic and therapeutic composition containing benzilic acid as the only active ingredient for oily skin, acne, skin cleansing and skin malodor may be formulated as follows.

Benzilic acid 7 grams is dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 13 ml with stirring until a clear solution is obtained. The composition thus prepared contains 7% benzilic acid, and has pH 3.0.

EXAMPLE 11

A therapeutic composition containing tropic acid as the only active ingredient for severe dry skin may be formulated as follows.

Tropic acid 10 grams is dissolved in 20 ml of ethanol, and the solution thus obtained is mixed with 70 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 10% tropic acid as an active ingredient, and has pH 3.7.

EXAMPLE 12

A prophylactic and therapeutic composition containing ribonolactone as the only active ingredient for oily skin, acne and skin cleansing may be formulated as follows.

Ribonolactone 4 grams is dissolved in a mixture of ethanol 36 ml and water 60 ml with stirring until a clear solution is obtained. The composition thus prepared contains 4% ribonolactone as an active ingredient, and has pH 3.8.

EXAMPLE 13

A therapeutic composition containing hydrocortisone and tropic acid for inflammatory and/or pruritic skin disorders may be formulated as follows.

Hydrocortisone 0.5 gram and tropic acid 5 grams are dissolved in 10 ml of ethanol and 4 ml of acetone, and the solution thus obtained is mixed with 80 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 0.5% hydrocortisone and 5% tropic acid as active ingredients, and has pH 3.4. The tropic acid has been added to enhance the penetration and the efficacy of hydrocortisone and also to normalize the disturbed keratinization.

EXAMPLE 14

A therapeutic composition containing triamcinolone acetonide and benzilic acid for eczema, psoriasis and other inflammatory and pruritic skin disorders may be formulated as follows.

Triamcinolone acetonide 0.1 gram and benzilic acid 5 grams are dissolved in 10 ml of ethanol, and the solution thus obtained is mixed with 85 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 0.1% triamcinolone acetonide, 5% benzilic acid, and has pH 3.4. The benzilic acid has been added to enhance the penetration and the efficacy of triamcinolone acetonide, and also to normalize the disturbed keratinization in eczema, psoriasis and other inflammatory skin disorders.

EXAMPLE 15

A prophylactic and therapeutic composition containing dipyridamole and lactic acid for hair growth and for prevention of hair loss on the scalp may be formulated as follows.

Dipyridamole 2 grams and lactic acid 4 ml are dissolved in a mixture of ethanol 80 ml and propylene glycol 14 ml with stirring until a clear yellowish solution is obtained. The composition thus formulated contains 2% dipyridamole, 4% lactic acid, and has pH 4.4. The lactic acid has been added to help dipyridamole dissolved into solution, to enhance the penetration and the efficacy of dipyridamole for hair growth and for preventing hair loss.

EXAMPLE 16

A therapeutic composition containing clobetasol propionate and agaricic acid for eczema, psoriasis and other inflammatory and pruritic skin disorders may be formulated as follows.

Agaricic acid fine powder 2 grams and 98 grams of clobetasol propionate cream are mixed until a uniform consistency is obtained. the composition thus formulated contains approximately 0.05% clobetasol propionate, 2% agaricic acid, and has pH 4.3. The agaricic acid has been added to enhance the penetration and the efficacy of clobetasol propionate, and also to normalize the disturbed keratinization in eczema, psoriasis and other inflammatory skin disorders.

EXAMPLE 17

A therapeutic composition containing betamethasone dipropionate and benzilic acid for eczema, psoriasis, contact dermatitis and other inflammatory and pruritic skin disorders may be formulated as follows.

Benzilic acid powder 5 grams and 95 grams of betamethasone dipropionate ointment are mixed until a uniform consistency is obtained. the composition thus formulated contains approximately 0.05% betamethasone dipropionate and 5% benzilic acid. The benzilic

acid has been added to enhance the penetration and the efficacy of betamethasone dipropionate, and also to normalize the disturbed keratinization in eczema, psoriasis and other inflammatory skin disorders.

EXAMPLE 18

A prophylactic and therapeutic composition containing aloe, malic acid and gluconolactone for oily skin and acne may be formulated as follows.

Aloe powder 200 fold 0.2 gram and ammoniated glycyrrhizinate 2 grams are mixed with water 61 ml and propylene glycol 2 ml. The mixture is heated to 50° C. until the aloe powder and the ammoniated glycyrrhizinate are completely dissolved. Ethanol 10 ml is added to the solution followed by the addition of partially neutralized malic acid stock solution 3 ml and gluconolactone stock solution 22 ml with stirring. The warm solution is poured into container jars before cooling. The gel composition thus formulated contains 40% aloe, 1% malic acid, 9% gluconolactone, and has pH 4.0. Malic acid and gluconolactone have been added to enhance the skin softness and smoothness by aloe, and also to normalize any disturbed keratinization of the skin.

EXAMPLE 19

A sun screen composition containing Octyl dimethyl PABA, dioxybenzone and lactic acid may be formulated as follows. Octyl dimethyl PABA 5 grams, dioxybenzone 3 grams and lactic acid 2 ml are dissolved in a mixture of ethanol 65 ml, water 10 ml and propylene glycol 15 ml with stirring until a clear solution is obtained. The composition thus formulated contains 5% octyl dimethyl PABA, 3% dioxybenzone, 2% lactic acid, and has pH 3.6. The lactic acid has been added to substantiate the absorption of sunscreen agents, octyl dimethyl PABA and dioxybenzone, and to enhance the sun screen effect.

EXAMPLE 20

A prophylactic and therapeutic composition containing tetracycline and glycolic acid for oily skin and-acne may be formulated as follows.

Tetracycline 3 grams and glycolic acid 5 grams are dissolved in a mixture of ethanol 40 ml, water 40 ml and propylene glycol 12 ml with stirring until the tetracycline and glycolic acid are completely dissolved. The composition thus formulated contains 3% tetracycline, 5% glycolic acid, and has pH 3.4. The glycolic acid has been added to help tetracycline dissolved into the solution, to enhance the penetration and the efficacy of tetracycline, and to normalize the disturbed keratinization in acne.

EXAMPLE 21

A therapeutic composition containing griseofulvin and methyl pyruvate for fungal infection of nails may be formulated at follows.

Griseofulvin 1 gram and methyl pyruvate 2 ml are dissolved in a mixture of 2-pyrrolidone 20 ml. PEG-400 47 ml and ethanol 30 ml with stirring until the griseofulvin is completely dissolved. The composition thus formulated contains 1% griseofulvin, 2% methyl pyruvate, and has pH 4.4. The methyl pyruvate has been added to help griseofulvin dissolve into the solution, to enhance the penetration and the efficacy of griseofulvin, and to normalize the disturbed keratinization in nails.

EXAMPLE 22

A therapeutic composition containing lidocaine and atrolactic acid for pruritic skin may be formulated as follows.

Lidocaine 2 grams and atrolactic acid hemihydrate 3 grams are dissolved in a mixture of ethanol 40 ml, water 40 ml and propylene glycol 15 ml with stirring until the lidocaine and atrolactic acid are completely dissolved. The composition thus formulated contains 2% lidocaine, 3% atrolactic acid, and has pH 4.6. The atrolactic acid has been added to help lidocaine dissolved and stabilized in the solution and to enhance the efficacy of lidocaine for pruritic skin.

EXAMPLE 23

A prophylactic and therapeutic composition containing retinoic acid and ethyl pyruvate for oily skin and acne may be formulated as follows.

Retinoic acid, all-trans 0.1 gram and ethyl pyruvate 2 ml are dissolved in a mixture of ethanol 80 ml, water 10 ml and propylene glycol 8 ml with stirring until a yellowish solution is obtained. The composition thus formulated contains 0.1% vitamin A acid, 2% ethyl pyruvate, and has pH 3.6. The ethyl pyruvate has been added to enhance the penetration and the efficacy of retinoic acid, and to normalize the disturbed keratinization in acne.

EXAMPLE 24

A prophylactic and therapeutic composition containing erythromycin and aleuritic acid for oily skin and acne may be formulated as follows.

Erythromycin 2 grams and aleuritic acid 2 grams are dissolved in a mixture of ethanol 50 ml, water 40 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The composition thus formulated contains 2% erythromycin, 2% aleuritic acid, and has pH 5.7. The aleuritic acid has been added to help erythromycin dissolve into the solution, to enhance the penetration and the efficacy of erythromycin, and to normalize the disturbed keratinization in acne.

EXAMPLE 25

A therapeutic composition containing P-hydroxymandelic acid for dry skin may be formulated as follows.

P-Hydroxymandelic acid 10 grams is dissolved in 20 ml of ethanol, and the pinkish solution thus obtained is mixed with 70 grams of hydrophilic ointment USP with stirring until a uniform consistency is obtained. The composition thus formulated contains 10% P-hydroxymandelic acid as an active ingredient, and has pH 3.2. P-Hydroxymandelic acid has been incorporated into the composition to alleviate any scaly or flaky skin, and to change the dry skin into normal smooth and soft skin.

EXAMPLE 26

A therapeutic composition containing hydroquinone and lactic acid in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The composition thus formulated contains 4% hydroquinone, 10% lactic acid, and has pH 4.0. The lactic acid has

been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

EXAMPLE 27

A therapeutic composition containing hydroquinone and glycolic acid in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The composition thus formulated contains 5% hydroquinone, 8% glycolic acid, and has pH 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

EXAMPLE 28

A therapeutic composition containing hydroquinone and 2-methyl 2-hydroxypropanoic acid in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The composition thus formulated contains 4% hydroquinone, 12% 2-methyl 2-hydroxypropanoic acid, and has pH 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

EXAMPLE 29

A composition containing hydroquinone alone in solution form for age spots and keratoses studies may be formulated as follows.

Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The composition thus prepared contains 5% hydroquinone and has pH 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

TEST RESULTS

In order to determine whether addition of a hydroxyacid in the composition could enhance the therapeutic action of a cosmetic or pharmaceutical agent a total of more than 55 volunteers and patients having different skin disorders participated in these studies. Each participating subject was given two preparations; i.e. with or without the addition of a hydroxyacid in the therapeutic composition.

Topical applications were carried out either by bilateral or sequential comparison, In bilateral comparison the subject was instructed to apply one preparation on one side of the body and the other one on the other side of the body. For psoriasis, eczema, severe dry skin, athlete's foot, etc., where both sides were involved, the subject was instructed to apply two to three times daily one medication on one side of the body for a period of up to several months of time. In the pulse treatment for psoriasis or other inflammatory diseases the medication was applied only once every three days or twice a week. The medication was discontinued whenever a total remission of the lesions occurred prior to the test period of up to several months.

For the scalp or face involvement such as in dandruff, oily skin, acne and seborrheic dermatitis the subject was instructed to apply two to three time daily one medication on one side of the scalp or the face and the other medication on the other side of the scalp or the face for a period of up to 12 weeks of time. For age spots, keratoses or warts the medication was continued for up to 4 months of time.

Sequential administrations of medications were carried out whenever the bilateral comparison was difficult. for example in pruritic conditions the subject was instructed to apply four time daily or as often as necessary one medication on the pruritic lesions for two days, then switched to the other medication on the same lesions for another two days, thus to compare which medication was more effective in relieving the itching.

1. Dry skin.

Human subjects having ordinary dry skin or with moderate degrees of dry skin as evidenced by dry, flaking and cracking of the skin were instructed to apply topically the lotion, cream or ointment containing 3 to 7 percent of hydroxyacids of the instant invention on the affected skin areas. Topical application, two to three times daily, was continued for two to three weeks. In all the nine subjects tested, the feeling of the skin dryness disappeared within a week of topical application. The rough and cracked skin became less pronounced and the skin appeared normal and felt smooth after 10 days of topical treatment.

The ordinary dry skin conditions once restored to normal appearing skin remained improved for some time until causes of dry skin, such as low humidity, cold weather, excessive contact pressure, detergents, soaps, solvents, chemicals, etc., again caused recurrence of the dry skin condition. On continued use it was also found that twice daily topical application of a composition containing one or more hydroxyacids of instant invention prevented the development of new dry skin lesions.

In severe dry skin the skin lesions are different from the above. The involved skin is hyperplastic, fissured and has thick adherent scales. The degree of thickening is such that lesions are palpably and visually elevated. The thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. The two attributes of thickness and texture can be quantified to allow objective measurement of degree of improvement from topically applied therapeutic test materials as follows:

| | DEGREE OF IMPROVEMENT | | | | |
|---|---|---|---|---|---|
| | None (0) | Mild (1+) | Moderate (2+) | Substantial (3+) | Complete (4+) |
| THICKNESS | Highly elevated | Detectable reduction | Readily apparent reduction | Barely elevated | Normal thickness |
| TEXTURE | Visibly rough | Palpably rough | Uneven but not rough | Slightly uneven | Visibly and palpably smooth |

By means of such parameters degrees of change in lesions can be numerically noted and comparisons made of one treated site to another.

In order to evaluate the hydroxyacids and their related compounds of the instant invention a total of six patients with severe dry skin conditions or ichthyosis were treated with the compositions containing 7 to 15% of hydroxyacids as described in the Examples.

Treated areas were of a size convenient for topical applications, i.e., circles 5 cm in diameter demarcated with a plastic ring of that size inked on a stamp pad. The medicinal creams or ointments were topically applied by the patient in an amount sufficient to cover the treatment sites. Applications were made three time daily and without occlusive dressings. Applications were discontinued at any time when resolution of the lesion on the treatment area was clinically judged to be complete.

The test results on patients with severe dry skin are summarized on the following table.

Topical Effectiveness of Hydroxyacids on Severe Dry Skin

| Compounds | Number of Patients | Therapeutic Effectiveness |
|---|---|---|
| 1. Tropic acid | 4 | 4+ |
| 2. Benzilic acid | 5 | 4+ |
| 3. Ribonolactone | 3 | 3+ |
| 4. 4-Hydroxymandelic acid | 2 | 3+ |
| 5. 3-Chloro 4-hydroxymandelic acid | 2 | 3+ |
| 6. 3,4-Dihydroxymandelic acid | 2 | 3+ |

2. Psoriasis

The involved skin in psoriasis is hyperplastic (thickened), erythematous (red or inflamed), and has thick adherent scales. the degree of thickening is such that lesions are elevated up to 1 mm above the surface of adjacent normal skin; erythema is usually an intense red; the thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These three attributes of thickness, color and texture can be quantified to allow objective measurement of degree of improvement from topically applied therapeutic test materials as follows.

| | DEGREE OF IMPROVEMENT | | | | |
|---|---|---|---|---|---|
| | None (0) | Mild (1+) | Moderate (2+) | Substantial (3+) | Complete (4+) |
| Thickness | Highly elevated | Detectable reduction | Readily apparent | Barely elevated | Normal thickness |
| Texture | Visibly rough | Palpably rough | Uneven but not rough | Slightly uneven | Visibly and palpably smooth |
| Color | Intense red | Red | Dark Pink | Light pink | Normal skin color |

By means of such parameters degree of improvements in psoriatic lesions can be numerically recorded and comparisons made of one treated site to another. The treatment schedule was quite different from the previously described in that the present study was employing a "Pulse Treatment." Instead of several times daily application the therapeutic composition of antipsoriatic agent with or without a hydroxyacid in solution form was topically applied to the involved skin only once in every three days or twice a week. The test results on patients having psoriasis are summarized on the following table.

Topical Effects on Psoriasis of Antipsoriatic Agents With or without Hydroxyacids

| Compositions | Number of Patients | Therapeutic Effectiveness |
|---|---|---|
| Thionicotinamide 3% alone | 6 | 2+ |
| with 10% Lactic acid | 6 | 4+ |
| with 5% Glycolic acid | 4 | 4+ |
| with 5% 2-methyl 2-hydroxypropanoic acid | 3 | 4+ |
| 6-Aminonicotinamide 1% alone | 5 | 3+ |
| with 10% Lactic acid | 5 | 4+ |
| with 10% Glycolic acid | 4 | 4+ |
| Betamethasone dipropionate 0.05% ointment alone | 5 | 3+ |
| with 5% Benzilic acid | 4 | 4+ |
| with 5% Tropic acid | 3 | 4+ |
| with 5% 2-Methyl 2-Hydroxypropanoic acid | 3 | 4+ |
| Clobetasol propionate 0.05% cream alone | 4 | 2+ |
| with 5% Benzilic acid | 3 | 3+ |
| with 5% Tropic acid | 2 | 3+ |
| with 5% 2-Methyl 2-hydroxypropanoic acid | 3 | 3+ |

In a topical treatment of eczema patients, betamethasone dipropionate or clobetasol propionate alone at 0.05% would achieve only a 3+ improvement on all the eczema patients tested. As shown by the table with the additional of 5% gluconolactone or ribonolactone betamethasone dipropionate or clobetasol propionate could attain a 4+ maximal clearing on all the eczema patients tested.

Topical Effects on Eczema of Corticosteroids With and Without Hydroxyacid Lactone

| Composition | Number of Patients | Therapeutic Effectiveness |
|---|---|---|
| Betamethasone dipropionate 0.05% | 3 | 3+ |

-continued

Topical Effects on Eczema of Corticosteroids With and Without Hydroxyacid Lactone

| Composition | Number of Patients | Therapeutic Effectiveness |
|---|---|---|
| alone | | |
| with 5% Gluconolactone | 3 | 4+ |
| with 5% Ribonolactone | 2 | 4+ |
| Clobetasol propionate 0.05% alone | 4 | 3+ |
| with 5% Gluconolactone | 4 | 4+ |
| with 5% Ribonolactone | 3 | 4+ |

3. Age Spots, Wrinkles, Keratoses and Pigmented Skin lesions.

Therapeutic compositions packaged in felt pens as described in Examples were provided to 14 patients for treatment of age spots, wrinkles, keratoses and other pigmented skin spots. Each participating patient received two felt pens; i.e. with or without the addition of hydroxyacid to the composition containing hydroquinone. The patients were instructed to apply topically one medication on one side of the body such as on the back of the left hand and the other medication on the other side of the body such as on the back of the right hand. Specific instructions were given to the patients that the medications were applied twice daily and discretely only to the skin lesions of age spots, wrinkles, keratoses, melasmas, lentigines or other pigmented skin spots.

Within one to three weeks, improvement of age spots and keratoses was clinically discernible. After one to three months substantial eradication of age spots, wrinkles and keratoses occurred in all the patients tested. Complete eradication of age spots usually occurred within two to four months of topical administration in most cases. Therapeutic compositions containing higher concentrations of hydroxyacids (10 to 20%) and hydroquinone (3 to 5%) were judged to be more efficient in eradicating age spots, wrinkles and keratoses within shorter periods of time. Without the addition of a hydroxyacid to the composition of hydroquinone, eradication of age spots, wrinkles or keratoses did not occur within four months of time.

It was also found that while compositions containing hydroxyacids without hydroquinone were effective for eradication of keratoses and wrinkles, the compositions were not efficient in eradicating pigmented age spots, melasmas or lentigines within 4 months of time. In any case, with the addition of a hydroxyacid to the composition containing hydroquinone, pigmented age spots, melasmas, lentigines and other pigmented skin spots had been substantially eradicated.

4. Acne.

Therapeutic compositions containing tetracycline, erythromycin or chlorhexidine with or without the addition of a hydroxyacid were provided to 9 patients having papulopustular or pustular lesions of acne. Each participating patient received two medications, with or without the addition of a hydroxyacid to the composition containing an antibiotic. The patients were instructed to apply topically one medication on one side of the body such as the left side forehead, face, back or chest, and the other medication on the other side of the body such as right side forehead, face, back or chest. Twice daily administration was continued for 4 to 12 weeks.

The degree and rate of improvement on acne lesions were clinically evaluated, and comparison was made between the two sides; one side with and the other side without a hydroxyacid in the compositions containing an antibiotic. It was found that the degree and rate of improvement on acne lesions were substantially better on the side treated with a combination composition containing both the hydroxyacid and the antibiotic as compared to that of the antibiotic alone. The time for complete clearing of acne lesions treated with a combination composition varied from 4 to 12 weeks of time, with an average time of 8 weeks, whereas complete clearing with that of the antibiotic alone ranged from 8 weeks to 9 months, with an average of 4 months.

5. Preventing Hair Loss And For Hair Growth.

Prophylactic and therapeutic compositions containing minoxidil or dipyridamole with or without a hydroxyacid or related compound were provided to 6 human subjects having a progressive loss of hair on the scalp. Each participating subject received two medications; i.e. with or without the addition of a hydroxyacid to the composition containing minoxidil or dipyridamole. The subjects were instructed to apply topically one medication on one side of the scalp and the other medication on the other side of the scalp. Twice daily topical applications were continued for 2 to 6 months. Clinical evaluation shows that the combination compositions containing minoxidil or dipyridamole and a hydroxyacid or related compound were therapeutically more efficient in preventing the hair loss and enhancing hair growth on the scalp.

Therapeutic compositions containing clotrimazole or griseofulvin with or without the addition of a hydroxyacid were provided to 6 patients having recurrent fungal infections of the foot; i.e. athlete's foot with or without toe nail involvement. Each participating patient received two medications with or without the addition of a hydroxyacid to the composition containing clotrimazole or griseofulvin. The patients were instructed to apply topically one medication on one side of the body such as left foot, and the other medication-on the other side of the body such as right foot. Three time daily applications were continued for one to two weeks. When nail infections were involved the topical application was continued for up to 4 months using the compositions containing griseofulvin with or without the addition of a hydroxyacid.

The degree and rate of improvement on skin lesions were clinically evaluated, and comparison was made one side of the body against the other. It was found that the skin lesions improved much faster with the compositions containing both the antifungal agent and the hydroxyacid. The presence of hydroxyacid appeared to enhance the efficacy of the antifungal agent, and also to eliminate the discomforts such as itching, tingling, burning and heat due to the fungal infection. Generally the infected skin healed within a week from topical application of the compositions containing an antifungal agent and a hydroxyacid. When toe nails were involved in the fungal infection the complete healing and regrowth of nails usually took several months on continued topical application of medications containing griseofulvin and a hydroxyacid.

The hydroxyacids and related compounds which may be useful as dermatologic agents for various conditions and disorders including age spots, keratoses, skin wrinkles etc. or as additives to enhance therapeutic effects of other cosmetic or pharmaceutical agents include 2-Hydroxyacetic acid; 2-hydroxypropanoic acid; 2-methyl 2-hydroxypropanoic acid; 2-hydroxybutanoic

acid; phenyl 2-hydroxyacetic acid; phenyl 2-methyl 2-hydroxyacetic acid; 3-phenyl 2-hydroxyacetic acid; 2,3-dihyroxypropanoic acid; 2,3,4-trihydroxybutanoic acid; 2,3,4,5,6-pentahydroxyhexanoic acid; 2-hydroxydodecanoic acid; 2,3,4,5-tetrahydroxypentanoic acid; 2,3,4,5,6,7-hexahydroxyheptanoic acid; diphenyl 2-hydroxyacetic acid; 4-hydroxymandelic acid; 4-chloromandelic acid; 3-hydroxybutanoic acid; 4-hydroxybutanoic acid; 2-hydroxyhexanoic acid; 5-hydroxydodecanoic acid; 12-hydroxydodecanoic acid; 10-hydroxydecanoic acid; 16-hydroxyhexadecanoic acid; 2-hydroxy-3-methylbutanoic acid; 2-hydroxy-4-methylpentanoic acid; 3-hydroxy-4-methoxymandelic acid; 4-hydroxy-3-methoxymandelic acid; 2-hydroxy-2-methylbutanoic acid; 3-(2-hydroxphenyl) lactic acid; 3-(4-hydroxyphenyl) lactic acid; hexahydromandelic acid; 3-hydroxy-3-methylpentanoic acid; 4-hydroxydecanoic acid; 5-hydroxydecanoic acid; aleuritic acid.

2-Hydroxypropanedioic acid; 2-hydroxybutanedioic acid; erythraric acid; threaric acid; arabiraric acid; ribaric acid; xylaric acid; lyxaric acid; glucaric acid; galactaric acid; mannaric acid; gularic acid; allaric acid; altraric acid; idaric acid; talaric acid; 2-hydroxy-2-methylbutanedioic acid.

Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, ascorbic acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, gulonolactone, mannonolactone, citramalic acid.

Pyruvic acid, hydroxypyruvic acid, hydroxypyruvic acid phosphate, their esters; methyl pyruvate, ethyl pyruvate, propyl pyruvate, isopropyl pyruvate; phenyl pyruvic acid, its esters; methyl phenyl pyruvate, ethyl phenyl pyruvate, propyl phenyl pyruvate; formyl formic acid; its esters; methyl formyl formate, ethyl formyl formate, propyl formyl formate; benzoyl formic acid, its esters; methyl benzoyl formate, ethyl benzoyl formate and propyl benzoyl formate; 4-hydroxybenzoyl formic acid, its esters; 4-hydroxyphenyl pyruvic acid, its esters; 2-hydroxyphenyl pyruvic acid and its esters.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims and all changes which come within the meaning and equivalency of the claims are therefore intended to be embraced therein.

What is claimed is:

**1**. Method of visibly reducing a human skin wrinkle comprising topically applying to said wrinkle a composition comprising 2-hydroxyethanoic acid (glycolic acid), or a topically effective salt thereof, in an amount and for a period of time sufficient to visibly reduce said wrinkle.

**2**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid is in the form of a free acid.

**3**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid is in salt form.

**4**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid or topically effective salt thereof is applied periodically for a period of time sufficient to achieve at least a clinically discernable reduction of said wrinkle.

**5**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid or topically effective salt thereof is applied periodically for a period of time sufficient to achieve at least a substantial eradication of said wrinkle.

**6**. The method according to claim **1**, wherein said period of time is at least three months.

**7**. The method according to claim **1**, wherein said period of time is at least four months.

**8**. The method according to claim **1**, wherein said topical application is on a daily basis.

**9**. The method according to claim **1**, wherein said 2-hydroxyethanoic acid or topically effective salt thereof is present in a topically acceptable composition comprising a carrier.

**10**. The method according to claim **9**, wherein said composition is a lotion, cream, gel, ointment or solution.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 5,389,677
DATED : February 14, 1995
INVENTOR(S) : Yu et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, item [54] and column 1, "GLYCALIC" should read --GLYCOLIC--.

Signed and Sealed this

Eighteenth Day of April, 1995

*Attest:*

*Attesting Officer*

BRUCE LEHMAN

*Commissioner of Patents and Trademarks*

[redacted]

US005389677B1

# REEXAMINATION CERTIFICATE (3270th)

**United States Patent** [19] [11] **B1 5,389,677**

**Yu et al.** [45] Certificate Issued ***Jul. 15, 1997**

[54] **METHOD OF TREATING WRINKLES USING GLYCALIC ACID**

[75] Inventors: **Ruey J. Yu**, Ambler; **Eugene J. Van Scott**, Abington, both of Pa.

[73] Assignee: **Tristrata, Incorporated**, Princeton, N.J.

**Reexamination Request:**
No. 90/004,432, Oct. 28, 1996

**Reexamination Certificate for:**

| | |
|---|---|
| Patent No.: | **5,389,677** |
| Issued: | **Feb. 14, 1995** |
| Appl. No.: | **89,101** |
| Filed: | **Jul. 12, 1993** |

[*] Notice: The portion of the term of this patent subsequent to Feb. 25, 2009, has been disclaimed.

**Related U.S. Application Data**

[62] Division of Ser. No. 8,223, Jan. 22, 1993, which is a continuation of Ser. No. 812,858, Dec. 23, 1991, abandoned, which is a continuation of Ser. No. 469,738, Jan. 19, 1990, abandoned, which is a continuation of Ser. No. 945,680, Dec. 23, 1986, abandoned.

[51] **Int. Cl.**[6] ..... **A61K 31/19**; A61K 7/48

[52] **U.S. Cl.** ..... **514/557**; 514/844; 514/847; 514/873

[58] **Field of Search** ..... 514/557, 844, 514/847, 873

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,197,316 4/1980 Yu et al. ..... 424/317

FOREIGN PATENT DOCUMENTS

1439834 4/1966 France .

OTHER PUBLICATIONS

K. Bergwein, *Kosmetik*, No. 16, pp. 556–557 (1967)—English translation.

Handbook of Chemistry and Physics, C.D. Hodgmen et al, 41st ed., pp. 1753–1756, CRC Press, Cleveland, Ohio (1962).

*Primary Examiner*—James J. Seidleck

[57] **ABSTRACT**

Composition and method for enhancing therapeutic effects of topically applied agents are disclosed. The cosmetic or therapeutic composition may include one or more of cosmetic or pharmaceutical agents present in a total amount of from 0.01 to 40 percent and one or more of hydroxycarboxylic acids or related compounds present in a total amount of from 0.01 to 99 percent by weight of the total composition. The cosmetic and pharmaceutical agents may include but not limited to age spots, wrinkles and keratoses removing agents; vitamins; aloes; sun screens; tanning, depigmenting and shampooing agents; antiyeasts; antifungal, antibacterial and antiviral agents; topical bronchial dilators and topical cardiovascular agents; hormonal agents; vasodilators; retinoids and other dermatological agents. The hydroxycarboxylic acids and related compounds include organic alpha and beta hydroxycarboxylic acids, alpha and beta ketocarboxylic acids and salts thereof. Topical application of the cosmetic or therapeutic composition has been found to achieve a substantial increase in cosmetic or therapeutic effect of the active ingredient in human and domesticated animals.

## REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT



AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1–10** is confirmed.

* * * * *

JS44

# CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by the Rules of Court. This form, approved by the Judicial Conference of the united States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the Civil Docket Sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

## I. (a) PLAINTIFFS

**Tristrata Technology, Inc.**

**(b)** COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
EXCEPT IN U.S. PLAINTIFF CASES)
Leatherhead, Surrey, England

**(c)** ATTORNEYS FIRM NAME, ADDRESS AND PHONE NO.
**Connolly Bove Lodge & Hutz LLP, 1007 N. Orange Street, PO Box 2207, Wilmington, DE 19899, Timothy M. Holly, Esq., (302) 658-9141**

## DEFENDANTS

**Jeunique International, Inc., et al.**

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED

ATTORNEYS (IF KNOWN)

## II. BASIS OF JURISDICTION (PLACE AN "X" IN ONE BOX ONLY)

- ☐1 U. S. Government Plaintiff
- [X]3 Federal Question (U. S. Government Not A Party)
- ☐2 U. S. Government Defendant
- [] Diversity (Indicate Citizenship of Parties in Item III)

## III. CITIZENSHIP OF PRINCIPAL PARTIES

(PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)

| | PTF | DEF | | PTF | DEF |
|---|---|---|---|---|---|
| Citizen of This State | [X]1 | ☐1 | Incorporated or Principal Place of Business in This State | [X]4 | ☐4 |
| Citizen of Another State | ☐2 | [X]2 | Incorporated and Principal Place of Business in Another State | ☐5 | [X]5 |
| Citizen or Subject of a Foreign Country | ☐3 | ☐3 | Foreign Nation | ☐6 | ☐6 |

## IV. ORIGIN

*(PLACE AN "X" IN ONE BOX ONLY)*

[X]1 Original Proceeding | ☐2 Removed from State Court | ☐3 Remanded from Appellate Court | ☐4 Reinstated or Reopened | ☐5 Another District (specify) Transferred from | ☐6 Multidistrict Litigation | ☐7 Magistrate Judgment Appeal to District Judge from

## V. NATURE OF SUIT *(PLACE AN "X" IN ONE BOX ONLY)*

**CONTRACT**
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- [x] 190 Other Contract
- ☐ 195 Contract Product Liability

**REAL PROPERTY**
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

**TORTS**

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

**CIVIL RIGHTS**
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

**PERSONAL INJURY**
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 366 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

**PRISONER PETITIONS**
- ☐ 510 Motions to Vacate Sentence Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Other

**FORFEITURE/PENALTY**
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

**LABOR**
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

**BANKRUPTCY**
- ☐ 422 Appeal
- ☐ 443 Withdrawal 28 USC 157

**PROPERTY RIGHTS**
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☐ 840 Trademark

**SOCIAL SECURITY**
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

**FEDERAL TAX SUITS**
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

**OTHER STATUTES**
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of InformationAct
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

## VI. CAUSE OF ACTION

(CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE. DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY) **35 U.S.C. § 100,** *et seq* - willful and deliberate Infringement

## VII. REQUESTED IN COMPLAINT:

**DEMAND $ Damages and Injunctive relief**

CHECK IF THIS IS A **CLASS ACTION** ☐ UNDER F.R.C.P. 23

CHECK YES only if demanded in complaint:

**JURY DEMAND:** ☒ YES ☐ NO

## VIII. RELATED CASE(S) IF ANY (See instructions)

*Tristrata Technology, Inc. v. Milbar Laboratories, Inc.*, C.A. No. 05-801 (JJF)

DATE: October 17, 2006

SIGNATURE OF ATTORNEY OF RECORD Tim M. Holly (#4106)

FOR OFFICE USE ONLY
RECEIPT #_____ AMOUNT_____ APPLYING IFP_____ JUDGE_____ MAG. JUDGE_____

JS 44 Reverse

## INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44

Authority for Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently a civil cover sheet is submitted to the clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

**I. (a) Plaintiffs-Defendants.** Enter names (last, first middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency identify first the agency and then the official, giving both name and title.

**(b) County of Residence.** For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

**(c) Attorneys.** Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

**II. Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdiction be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

**III. Residence (citizenship) of Principal Parties.** This section of the JS-44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

**IV. Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause.

**V. Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable thedeputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

**VI. Origin.** Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers of multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

**VII. Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

**VIII. Related Cases.** This section of the JS-44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.
**Date and Attorney Signature.** Date and sign the civil cover sheet.

125334v1(CB)

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 06-645

# ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

## *NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION*

I HEREBY ACKNOWLEDGE RECEIPT OF 4 COPIES OF AO FORM 85.

10/17/06
(Date forms issued)

(Signature of Party or their Representative)

FRANK JOYCE / PARCELS, INC.
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action